CONGESTIVE HEART FAILURE

Heart failure definition

- Mechanical failure of the heart to maintain systemic perfusion commensurate w/ the requirements of metabolizing tissues.
- Inability of the heart to generate sufficient CO to meet the metabolic demands of the body –pump failure

Compensation Mechanisms For Increased Demands on the heart

- Frank Starling Mechanism
  - Increased Pressure→ increased preload of dilation (increased cross-bridges within the sarcomeres)
  - Enhances contractility b/c it ↑ the affinity of troponin C to calcium
- Myocardial Structural Changes
  - Augmented muscle mass (hypertrophy) w/ or w/o dilation
    - The COLLECTIVE molecular, cellular and structural CHANGES that occur as a result of injury are called **VENTRICULAR REMODELING!** ← Heart failure compensation
- Activation of Neurohumoral Systems
  - Release of the neurotransmitter NE by adrenergic cardiac nerves which increases contractility (through B1)
  - These two act to adjust filling volumes and pressures:
    - Activatino of the RAAS
    - Release of ANP→ diuretic & a vasodilator so it gets rid of the extra water load and vasodilates.

Causes of Cardiac dysfunction

- Pump failure
  - Forward failure
    - Problem with the CO
    - Not pushing enough blood out
  - Backward failure
    - Damming back of blood in the venous system
    - Cant pull blood back from the periphery to the heart
- Regurgitant Flow
- Obstruction to flow
- Conduction disorders—heart block
- Disruption of the circulatory system—shock, severe bleed, ↓ in blood volume

Progression of Hypertrophy to heart failure

- HTN (pressure overload), Valvular Dz (pressure and/or volume overload), MI (regional dysfunction w/ volume overload)→ ↑ cardiac work → ↑ wall stretch (Frank-starling) → cell stretch→ Hypertrophy and/or dilation (characterized by: ↑ heart size and mass, ↑ protein synth, induction of IE genes, induction of fetal gene program, abn proteins, fibrosis, inaquete vasculature)→ Cardiac dysfunction (characterized by heart failure (systolic/diastolic), arrhythmias, neurohumoral stimulation)

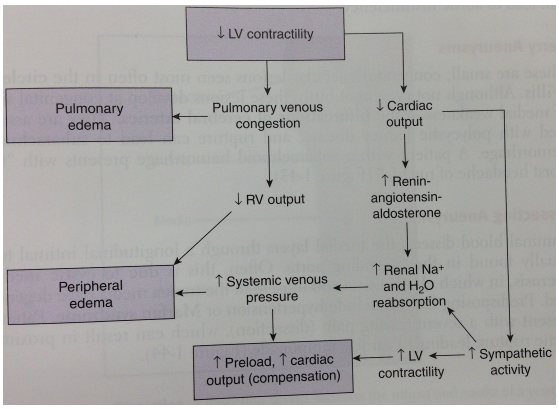
Left Sided Heart Failure

- Causes
  - Systolic Dysfunction
    - Impaired contractility
      - **Ischemic heart dz**
        - **b/c your replacing muscle w/ fibrous tissue**
      - MI
      - **Myocardial Dz**
        - **Pericarditis, viral myocarditis, amyloidosis**
      - Volume Overload, mitral or aortic regurg
    - Increased Afterload
      - **HTN # 1**
      - **Aortic stenosis**
      - Hypertrophic cardiomyopathy (HCM)
  - Diastolic dysfunction
    - Ventricular relaxation (stiff LV→ doesn't relax during diastole)

        - Ventricular hypertrophy
        - Cardiomyopathy
        - **Myocardial ischmia**
    - Impaired ventricular filling (can cause amyloidosis, fibrosis, and severe hypertrophy)
        - **Mitral stenosis**
        - Tamponade
        - Pericardial constriction
- Signs and Symptoms
    - Dyspnea on exertion (due to failure of CO to ↑ during exercise), **Paroxysmal nocturnal Dyspnea (more severe dyspnea at night)**, **orthopnea**, pulmonary edema, reduced renal perfusion and an S3 heart sound
        - Orthopnea→ Can breathe while lying flat so cant' sleep at night b/c when you lie flat the blood flows back to the venous system and heart cant handle it because it having pump failure so you prop yourself up so less blood goes to the heart b/c of gravity
- Morphology
    - Heart→ Hypertrophy
        - **if you see a dark brown color to heart and lots of brown pigment on autopsy→ **LIPOFUSCIN** –normal wear and tear on the heart
    - Lungs→ Congestion, edema (retention of blood and fluid in the lungs)
        - WILL SEE **HEART FAILURE CELLS—these are macrophages w/in the alveoli of the lungs that have phagocytosed hemosiderin (which is a hemoglobin breakdown product)**
    - Kidneys→ ↓ renal perfusion
        - Activation of RAAS → retention of salt and H20 → ↑ blood volume
    - Brain→ hypoxic encephalopathy
        - Not enough blood and O2 to the brain

Right Sided Heart Failure

- Usually the result of L-sided heart failure
- Pure R-sided heart failure (**cor pulmonale)** secondary to ↑ pulmonary pressure (like in COPD)
    - Cor pulmonale—alteration of the structure and function of the R-side of the heart secondary to chronic lung disorders, resulting in pulmonary arterial HTN
        - Right ventricular enlargement result from structural or functional lung disorders
        - Types:
            - Acute
                - Following massive PE
                - Markied dilatation of the RV
            - Chronic
                - Hypertrophy of the RV due to COPD, Fibrosis , Pulmonary vessel dz, Kyphosis, scoliosis, Metabolic acidosis, Hypoxia, etc
- Signs and symptoms
    - Liver
        - congestion (↑ LDH_5 b/c liver gets bigger due to congestion and dilation of sinusoids→ pressure necrosis of hepatocytes and the central veins→ LDH5 release)
            - **note: LDH1= RBC and heart
              LDH3= pulmonary infarct
              LDH5= liver
        - Cardiac sclerosis
        - Hepatomegaly (nutmeg liver)→ ↑ VCP→ resistance to portal flow. Rarely it will lead to cardiac cirrhosis
    - Congestive splenomegaly
    - Pleural effusion
        - R-sided HF fluid is in the pleural cavity and in L-sided HF fluid is in the alveoli
    - Ascites
    - **Peripheral edema** (cant drain blood well b/c of ↑ venous pressure)
    - Brain congestion and edema
    - Jugular venous distention (JVD) b/c of ↑ venous pressure

- 

Lab assessment of Heart Failure

- BNP
  - B-type Natriuretic Peptide
  - Regulates BP
  - If this value is high = CHF
    - >100 is high
  - If it is normal look for other causes of S.O.B.
  - Source : heart
  - Released into the blood in response to ↑ in BP

Cardiomyopathies (CMP)

- Heart muscle disease of unknown causes
- Diagnosed by cardiac bx
- 3 types
  - **Dilated (congestive) CMP**
    - MOST COMMON
    - Definition: progressive dilation and contractile systolic dysfunction
    - Causes **(ABCCCD)**
      - Idiopathic
      - **Alcohol abuse**
        - Direct toxicity
      - Thiamine deficiency (wet **B**eriBeri **Ber1Ber1—can be caused by deficiency of B1)
      - **C**oxsackie B virus infection
      - **C**hagas Dz (caused by T. cruzi and is transmitted by the reduviid bug)
      - HIV
      - **C**ocaine
      - **D**oxorubicin
      - Lyme dz
      - Sarcoidosis
      - Hypothyroidism
      - Wegner granulomatosis
      - Acromegaly
      - **Peripartum cardiomyopathy (WILL HAVE NORMAL BP)**
        - Manifests late in pregnancy for no apparent reason
        - ↑ levels of antiangiogenic cleavage product of prolactin
        - Nutritional
        - Immunological or hormornal
        - Tx: immediate delivery
        - *Be careful not to mistake for eclampsia (pts will have HTN)
      - **Genetics**
        - **MUTATION OF THE DYSTROPHIN GENE (CYTOSKELETAL PROTEIN)**
          - Plays a critical role linkng internal syotoskeleton w/ the external BM
          - Other genes: **α- CARDIAC ACTIN**
            - Links the sarcomere w/ dystrophin

- **Myocarditis**
- **Adriamycin toxicity (a chemotherapeutic agent)**

- Morphology
  - Heavy, flabby, soft heart
  - Dilated chambers
  - Thin wall
  - Microscopic
    - Large myocardial fibers and fibrosis
- Complications
  - Arrhythmias
  - Embolism (mural thrombi)
  - CHF, bundle branch blocks, and death

- **Hypertophic CMP= Idiopathic Hypertophic Subaortic Stenosis (IHSS)**
  - mostly LV and septum
  - usually GENETIC
    - Missense Mutation in the gene encoding β myosin heavy chain w/ the genes for cardiac **Troponin T, tropomyosin and and myosin binding protein (MYBPC)**
    - Autosomal dominant disorder in which **asymmetrical septal hypertrophy** (the septum below the aortic valve becomes hypertrophic) causes a decrease in LV compliance and diastolic dysfunction
  - Seen in young healthy ppl
  - Morphology
    - Thick heavy heart
    - Hypercontracting-no dilation
    - Disproportionate thickening of septum (asymmetrical)
    - Diastolic dysfunction (failure to relax)
    - Microscopic
      - HYPERTROPHY—large fibers w/ rectangular nuclei
      - DISARRAY
      - FIBROSIS
  - Clinical Picture
    - Impaired diastolic filling
    - Syncope
    - Harsh systolic ejection murmur—b/c area right below aortic valve is hypertrophied and acts like a stenosis
      - Blood flows at increased velocity over the hypertrophied septum, creating negative pressure, which draws the anterior mitral leaflet into the outflow tract thereby causing subaortic obstruction to outflow
      - **Any maneuver the ↓ EDV (like Valsalva maneuver or exercise) ↑ the murmur's intensity in both mitral valve prolapse (MVP) and HCM because the ↓ volume leads to a ↓ chamber size and ↑ obstruction

- **Restrictive/infiltrative**
  - Etiology
    - Caused by dz's that infiltrate the myocardium to impede diastolic filling of the heart
      - Common causes: sarcoidosis and amyloidosis
        - Amyloidosis—is a disorder in which amyloid light-chain protein fibers are deposited in tissues and organs, impeding their function
      - Endomycocardial fibrosis
      - **Loeffler's endocarditis w/ peripheral eosinophilia (most common worldwide)**
      - Endocardial fibroelastosis (left endocardium) –**children**
      - Others
        - Glycogen storage dzs (Pompe dz)
        - Inborn errors of metabolism (Fabry dz, Gaucher dz)
        - scleroderma
  - Clinical Picture
    - Dyspnea, weakness, exercise intolerance, peripheral edema, ascites, JVD, pulsus paradoxus, CDH, arrhythmias from conduction defect Functional defect

Hypertensive Heart Disease

- Hypertension Hypertrophy Heart Failure (HHHF) can lead to CHF
- Definition
  - LV hypertrophy
  - Absence of CV pathology
  - H/o HTN
    - ↑ BP (HTN)→ accelerated atherosclerosis → ↓ compliance of large BV's → thickening of small arteries and arterioles → ↑ Peripheral Resistance → Hypertrophy in order meet demands→ bigger heart = ↑ O2 demand and ↓ compliance
- Epidemiology
- Pathologic Lesions
  - Gross hypertrophy
  - Microscopic
    - Large rectangular nuclei (shoe boxes)
    - Hypertrophy

DISEASES OF THE ENDOCARDIUM

Rheumatic Fever

- Clinical Presentation
  - Febrile illness associated w/ acute inflammation (arthritis, etc), a rash, heart problems and a **previous SORE THROAT OR IMPETIGO (group A β-hemolytic strep)**
  - Seen in **children** age 5-15 (peaks at 6 years old)
  - Seasonal: Late winter and early spring (same as strep)
  - Physical Exams
    - Temperature 101
    - Pulse 100/min
    - Friction rub→ means pericarditis
- Systemic dz—effects more than 1 system
- Post-strept
- Nonsuppurative—not infectious = no bacteria so nothing will show up on culture
  - Thought that strep Ag's elicit production of Ab's that cross react w/ cardiac antigens
- Joint involvement→ common, benign reversible
- Heart involvement→ disabling irreversible
  - Early deaths are due to myocarditis
  - Late sequelae include rheumatic heart dz, which affects heart valves: mitral > arotic >> tricuspid
  - Early lesion is mitral valve regurg
  - Late lesion is mitral stenosis
- SO NEED TO PREVENT RF by treating STREP
- After Strep Pharyngitis (caused by strep pyogenes) effects:
  - Heart, joints, tendons, tendon sheaths, skin, serosal membranes, respiratory, vessels)
- Jones Criteria (2 major OR 1 major and 2 minor)
  - J<3NES (MAJOR CRITERIA)
    - **J**oint—arthritis
      - P.A.L.
        - Polyarthritis
        - Acute
        - Large Joints
    - **<3**—carditis (new onset murmur)
      - pancarditis
        - pericarditis
          - friction rub
          - sharp stabbing chest pain
            - **NOTE squeezing pain radiating to L should/arm = MI pain
              tearing pain radiating to back= aortic dissection

        - myocarditis
            - CHF
            - Cardiomegaly
        - Endocarditis
            - Murmur
    - SubQ **N**odules
        - Pea size PAINLESS swllings over bony prominences
            - Extensor tendons surfaces (Hands and feet)
            - Scalp-scapulae and spinous processes surfaces
    - **E**rythema Marginatum
        - Pink evanescent rash (press and redness goes away)
        - Clear center and red serpigenous margins (central pallor) on trunk—NEVER ON FACE
        - Transient migratory NONPRURITIC
    - **S**ydenham's Chorea
        - Sudden, aimless, irregular movement accompanied by muscle weakness and emotional instability (irritable)
        - Delated manifestation of RF
- Minor
    - Fever
    - Arthralgia (just pain no hot, red, or swollen)
    - ↑ ESR/CRP
    - ↑ PR interval on EKG
    - Leukocytosis (↑ WBC)
    - ASO titer
    - Anemia

- Lab Findings
    - ↑ ASO(anti-streptolysin O Test) titers (shows old strep infection)
        - 250 in adults
        - 333 in children
        - BUT 20% of patient w/ RF have low ASO titer
- Pathology
    - Myocarditis
        - Focal interstitial mycocardial inflammation (they are centered in the interstitum around vessels) in which collagen and fibrinoid material form nodules (**ASCHOFF BODIES—peculiar form of granulomatous inflammation; have both aschoff cells and anitschkow's cells**) and are surrounded by macrophages (**Anitschkow's cells→**activated histiocytes), lymphocytes, plasma cells and multinucleated giant cells **(Aschoff cells**)
        - Three phases of RF Lesions
            - Early—necrosis
            - Intermediate—proliferative
                - **Anitschkow's cells→ CATERPILLAR NUCLEUS**
                    - **Long thin cell w/ an elongated nucleus**
                - **Aschoff cells→ GIANT CELLS w/ OWL-EYE NUCLEUS**
                - Lymphocytes
                - Plasma cells
            - Late—healed
        - May be severe enough to cause CHF
    - Pericarditis
        - Diffuse, nonspecific
        - **FIBRINOUS**
            - Conditions that give you fibrinous pericarditis
                - Pot MI (Dresslers)
                - RF
                - Uremic pericarditis in chronic renal failure
            - Bread and butter pericarditis = friction rub
        - Can resolve or organize forming thickened plaques
        - Microscopically
            - Fibrin, lymphocytes, histiocytes, and occasional PMN's

- Endocarditis
  - The valve leaflets become red and swollen, and **small verrucae (warty, rubbery fibrin vegatations) form along the lines of closure on the side of blood flow.** Eventually when the endocarditis heals the valves become fibrotic, thickened, and calcified → A. **FISH MOUTH MITRAL VALVE,** B. **thickening and shortening of the chordae tendinaea,** C. **Map-like thicking of LA endocardium= McCallum's Patch**
    - Valvular dz can lead to either insufficiency of stenosis
    - Most often affect the **mitral** and **aortic** valves since they see the greatest pressure gradient
    - Chronic Rheumatic scarring (Fish Mouth Mitral Valve) Can lead to Rheumatic Fever Mitral Dz
      - When the lungs get so congested they may have a brownish color w/ heart failure (Will have congestion in the lungs b/c the lungs aren't draining and fluid is backing up)

- Course and Prognosis
  - Acute 75% → 6 weeks
  - Attack 90% → 12 weeks
  - 5% persists 6 months
  - 70% → carditis
- Cause of Death (chronic Rheumatic heart dz)
  - Mitral and aortic valvular fibrosis causes valve thickening and calcifications, fusions of commissures, and short, thick chordae tendineae. The chronic form can lead to
    - CHF due to valvular deformities
    - Mitral stenosis or regurg
    - Aortic Regurg
    - Can predispose to Bacterial endocarditis
    - Embolism
    - Sudden death—arrhythmia or coronary angitis

Infective Endocarditis

- Definition: Serious infectious dz characterized by colonization or invasion of heart valves or mural endocardium by microorganisms
- Heart valves are avascular so if bacteria adhere WBC's cannot be recruited to the area.
- Classification
  - Based on clinical background, virulence of microbe, the presence or absence of valvular dz
- Types
  - ACUTE
    - usually occurs on NORMAL VALVE
    - HIGHLY VIRULENT microbs (STAPH AUREUS)
    - Associated with IV DRUG USE
    - DESTRUVTIVE rapidly progressive course
    - Death w/in DAY→ WEEKS in spite of aggressive therapy
    - Pathology
      - Necrotizing lesions
      - Ulcerative lesions
      - Invasive lesions
  - SUBACUTE
    - Usually occurs on ABNORMAL/PREVIOUSLY DAMAGED VALVES
      - Associated w/ bacteremia from oral surgery or poor dentition
      - Valve abnormalities
        - Rheumatic Heart Disease
        - Myxomatous mitral valve—PROLAPSE
        - Calcific stenosis
        - Bicuspid valves
        - Prosthetic valves—S. epidermidis mostly effects w/in first 6 months after that S. aureus and viridans gropu strep are most likely culprits
    - LESS VIRULENT microbe (STREP—usually viridans group strep)
      - If the patient has h/o…
        - Dental work → viridans group strep
        - colon cancer then organisms is probably Strep bovis
        - GI surgery→ enterococcus
        - Total parenteral nutrition—fungal

        - Alcoholics or the homeless—bartonella henselae
        - Fastidious and culture negative→ HACEK organisms
            - Haemophilus
            - Actinobacillus
            - Cardiobacterium
            - Eikenella
            - Kingella
    - INDOLENT course (WEEKS→ MONTHS)
    - FULL RECOVERY w/ tx
    - Pathology
        - Less destructive lesion than acute type
    - Pathophysiology
        - High Velocity flow (due to abnormal valve) + Pressure gradient across Narrow orifice→ stripping endothelium → deposition of platelets and fibrin→ colonization w/ bacteria
- Host Factors Perpetuating IE
    - Neutropenia
    - Alcohol abuse
    - IV Drug use
        - R sided endocarditis suggests IV drug abuse since drugs are injected into the veins the bacteria go to the R heart first
    - Diabetes
      Immunospression
- Morphology
    - Gross
        - **FRIABLE (CAN BREAK OFF AND FORM ABSESS IN ANOTHER PLACE= SEPTIC INFARCT) BULKY VEGATATION** w/ destruction of underlying valves (especially in acute type)
    - Microscopic
        - Fibrin
        - Inflammatory cells
        - Bacteria
        - Granulation Tissue (subacute types)
            - Will see vascularization, fibrocytes, and lymphoblasts in granulation tissue (healing process)
- Complications
    - Erosion of myocardium (acute)
    - Systemic Emboli
    - Septic Infarcts
        - vessels around/in the brain are called mycotic aneurysms
- Clinical Picture/Presentation
    - Fever
    - Chills weight loss
    - Malaise
    - **IMMUNOOLOGIC** COMPLICATIONS—GLOMERULONEPHRITIS
    - Mechanical complications (murmurs)
        - Valvular involvement
            - Mitral> aortic > tricuspid
    - MICROEMBOLI
        - Petechiae
        - Janeway lesions
            - PAINLESS peripheral hemorrhages on the PALMS AND SOLES consequence of septic embolic events
        - Osler Nodes
            - Small PAINFUL subQ nodules on the FINGERS AND TOES
        - Splinter Hemorrhages
            - Linear streaks under the fingernails and toenails
        - Roth spots
            - Hemorrhagic spots on the retina
- Diagnosis
    - Blood cultures (must be repeated!)

- Echo (to demonstrate vegetations)
- DUKE CRITERIA (2 major; 1 major + 3 minor; 5 minor)
  - Major
    - Positive serial blood cultures
    - Valvular lesions on echo
    - New murmur
  - Minor
    - Predisposing heart lesion
    - IV drug use
    - Vascular lesion
      - arterial petechiae, subungual/splinter hemorrhages, emboli, septic infarcts, mycotic aneurysm, intracranial hemorrhage, Janeway lesions)
    - immunologic phenomena (glomerulonephritis)
    - Culture and echo

Non-Infective Endocarditis→ Marantic Endocarditis

- aka Nonbacterial thrombotic endocarditis (NBTE)
- occurs when small, sterile fibrin vegetation deposit on the heart valves of people w/ debilitating dz
- Tends to occur in ppl w/ a hypercoagulable state (**trousseau's sundrome)** →This is a paraneoplastic sx assoc. w/ malignancy in which mucin-secreting tumors (usually colon or pancreas) cause mucin deposition on the heart valves yielding a platelet-ticky nidus of infection
  - Usually **mucinous adenocarcinoma of the pancreas**
- Morphology
  - Gross **(along the lines of closure of the valves)**
    - Non-destructive
    - Sterile (not infective)
    - Small
  - Micro
    - Thrombi
    - No inflammation
    - No valve damage
- Pathologenesis
  - Underlying debilitating dz
  - Malignancies (especiialy mucinous adenocarcinoma of the pancrease—trousseau sign)
  - Hypercoagulable states
  - Sepsis
- Complication
  - STERILE EMOBLI—can lead to cerebral infarct
  - Poor prognosis

Libman-Sacks Endocarditis --SLE

- Autoantibody damage to the heart valves from SLE
- Small Sterile vegetations form on **BOTH SIDES OF THE HEART VALVES**!!!
- Fibrinoid necrosis
- **HEMATOXYLIN BODIES** –naked nuclei
- Pt is often asx, but the condition can be picked up by the presence of a heart murmur

Carcinoid Heart Disease

- Carcinoid tumors release ↑ amts of serotonin, which leads to thickening, contraction and decreased mobility of the R-sided valves, as well as BV dilation.
  - Involves the endocardium and valves of the R heart leading to thick plaques of SMC, collagen, fibrin, and **ACID MUCOPOLYSACCHARIDES w/ MATRIX**
- The L-sided heart is protected by serotonin inactivation in the lungs
- Carcinoid Syndrome
  - Group of symptoms assoc. w/ carcinoid tumor. Origin is most commonly the terminal ileum, and the tumor is large enough to cause systemic effects such as abd pain, flushing diarrhea, and wheezing
  - Flushing, asthma-like attacks, diarrhea, and a R-sided murmur. Occurs if the tumor metastasizes to the liver!

- Carcinoid Tumor
    - Most commonly found in the appendix but in general the tumor is too small to the asymptomatic
- Dx: ↑ 5-HIAA (serotonin metabolite), will see neurosecretory granules on EM

Mitral Valve Prolapse = MIDSYSTOLIC CLICK

- Synonyms
    - Floppy-valve syndrome
    - Barlow's syndrome
    - Myxomatous Degeneration
- Pathogenesis
    - Abnormalities in CT
- Clinical features
    - Mostly asx
    - mid-systolic click
    - usually found on echo
    - rarely chest pain
- Morphology
    - Gross
        - Ballooning of leaflets w/ elongated thing chordae
        - Rarely annular dilatation w/ resulting insufficiency
    - Micro
        - Attenuation of the fibrous layer of the valve
        - Thickening of the spongiosa layer
        - Myxomatous degeneration
- Complications
    - Rarely occurring
        - Infective endocarditis
        - Mitral insufficiency
        - Stroke or other systemic infarcts
        - Arrhythmias (both ventricular and atrial)

Calcified Aortic Stenosis

- Pathogenesis
    - Aging wear and tear
    - Will see hypertrophied heart
- Clinical features
    - Angina
    - CHF
    - **Syncope**
- Morphology
    - Calcification of vusps w/ resulting stenosis
    - Commonly seen in bicuspid valve (will present earlier in these patients—late 40's mid 50's)

Complications of Artificial Valves

- Thrombosis and thromboembolism
- Hemorrhage secondary to anti-coagulant therapy
- Endocarditis—subacute
- Intravascular hemolysis
- Leakage
- Obstruction
- Structural deterioration of mechanical valves or calcification of biosynthetic valves
- Microangiopathic hemolytic anemia
    - Can see schistocytes on peripheral blood smear

PERICARDIAL DISEASES

- The pericardium is a double layered sac that surrounds the heart, with the visceral pericardium lining the heart and the parietal pericardium on the outside. In between the two layers is pericardial fluid that helps to decrease friction

Pericardial Effusions

- ↑ fluid accumulation sometimes occurs in the pericardial space. The volume of fluid, the rate of increase and pericardial compliance all factor into the clinical symptoms
- Serous (transudate)
    - Usually passive accumulation
    - Low protein
    - No cells
- Purulent (exudate)
    - Active, something happening locally
    - INFECTIOUS
    - HIGH protein
    - MANY WBC's
- Malignant→ metastatic dz
    - Will have malignant cells

Hemopericardium

- Ruptured Myocardium
    - MI
        - Most risk post Mi is 5-7 days b/c end of acute inflammation and beginning of granulation tissue
            - soft, not strong
    - Trauma
- Aortic Dissection
    - HTN
    - Marfan Sx
- If severe >500 mL of blood
- It causes tamponade→ sudden death
    - Tamponade → pulsus paradoxydus (see EKG but cant feel pulse)
        - Beck triad of cadiac tamponade
            - Muffled heart sounds
            - Elevated JVP
            - Fall in systolic pressure

Causes of Pericarditis

- MNEMONIC
    - CARDIAC RIND
        - Collagen vascular dz
        - Aortic aneurysm
        - Radiation
        - Drugs (Hydralazine)
        - Infection
        - Acute renal failure
        - Cardiac infarction
        - Rheumatic fever
        - Injury
        - Neoplasms
        - Dresslers Syndrome
            - Delayed pericarditis that develops ~2 weeks after MI (autoimmune—antimyocardial Abs)
- Infectious Agents
    - Viruses
    - Pyogenic bacteria
    - Tuberculosis
    - Fungi

- Other parasites
- Presumably immunologically mediated
  - Rheumatic Fever
  - SLE
  - Scleroderma
  - Postcardiotomy
  - Post-MI (Dressler's) syndrome
    - 7-14 days
    - sharp pain
    - antibodies are antimyocardial antibodies
  - Drug hypersensitivity reaction
- Miscellaneous
  - Myocardial infarction
  - Uremia
  - Following cardiac surgery
  - Neoplasia
  - Trauma
  - Radiation

Types of Pericarditis

- Acute
  - Serous Pericarditis
    - Causes
      - Infectious (viral infections) –coxsackie B
      - Usually autoimmune dz
        - SLE, Rheumatoid Arthritis, Scleroderma
        - No major sequelae—usually pretty mild
      - Malignancy
    - Morphology
      - Exudate
        - Protein rich
        - Straw colored
        - Few inflammatory cells
      - Volume 50-200 mL
      - Scant inflammatory cells
  - **Fibrinous pericarditis**
    - Causes
      - Post-MI (dresslers) syndrome
      - Uremia
      - Rheumatic fever
      - Can lead to scar formation and diastolic filling defects
    - Clinical features
      - Sharp chest pain
      - Fever friction rub
    - Morphology
      - Exudate
        - Yellow cloud fluid
        - Fibrin-rich w/ plasma proteins
      - Rough epicardial surface
      - Fibrin, WBC's and RBC's
  - Purulent pericarditis
    - Exudate
      - Cloudy fluid w/ many inflammatory cells
    - Cause
      - Infectious bacteria
  - Hemorrhagic pericarditis
    - Exudate
      - Blood and inflammatory fluid

        - Causes
            - Malignancy
            - Bacterial infection--TB
            - Following cardiac surgery
        - **if you see blood in any body cavity your #1 on the Ddx should be tumor
    - Presentation
        - Retrosternal chest pain (worse on inspiration or coughing; relief while sitting or leaning forward)
        - Fever
        - Hypotension
        - JVD
        - Pericardial friction rub
        - Distant heart sounds
- Chronic
    - Gradual resorption of acute pericarditis can lead to fusion of the pericardial layers and scar formation w/ possible calcifications leading to a stiff pericardium → inhibition of diastolic filling and signs similar to those of CHF
        - Most common cause worldwide is Tb but may also be secondary to pyogenic organisms or staph spp. Leading to obliteration of the pericardial cavity
    - Adhesive Mediastino pericarditis
        - Follows suppurative inflammation or TB
            - Massive infection then healing
        - Sac obliterated and adhered to adjacent structures
            - Mediastinum replaced by scar so can have esophageal problems, respiratory problems, and heart problems
        - Increased strain on heart→ hypertrophy and/or dilatation
            - Pericardium is fibrotic so will present challenge to heart so the heart will have to hypertrophy
        - Can also occur post-radiotherapy to chest
            - Years after post RADIATION for hodgkins
    - Constrictive pericarditis (only pericardium involved)
        - Results from suppurative or hemorrhagic pericarditis (Staph or **TB)**
            - tuberculous pericarditis can produce extensive granulomatous inflammation with calcification that can severely restrict cardiac motion
        - Pericardial space obliterated by scar and/or calcification
            - Pericardium only involved, doesn't adhere! → its like the heart is encased in a hard shell so it will fail
        - Severe cardiac dysfunction (tamponade)
            - might behave like tamponade. so might have pulsus pardioxycus—EKG signs but no pulse
        - Heart is encased in a dense fibrocalcific scar that limits diastolic expansion
        - HEART SOUNDS ARE DISTANT AND MUFFLED
        - Mnemonic
            - Konstrictive pericarditis present w/ Kussmaul sign (jugular veins distend during inspiration) and a pericardial Knock (early apical diastolic sound)

VASCULAR NEOPLASMS

Telangiectasis

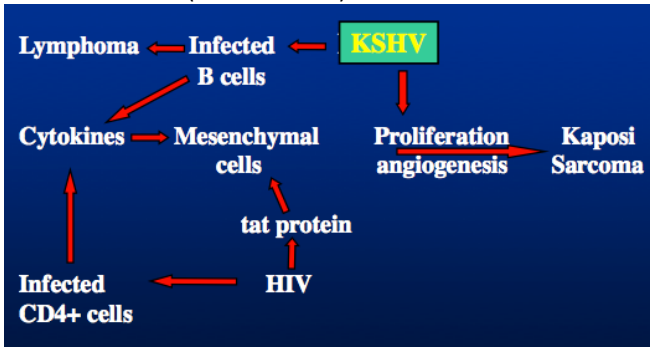
- Definition
    - A group of abnormally prominent capillaries, venules and arterioles that create small focal red lesions usually in skin and mucous membranes of the body
    - Ataxia telangiectasia is prob in T cells
        - Mutation in ATM gene which codes for DNA repair enzymes (double standed nonhomologous end joining)
            - Triad: cerebellar defects (ataxia), spider angiomas (telangiectasia), IgA deficiency
            - Labs: ↑ AFP
    - Similar to CREST Syndrome:
        - spectrum of scleroderma. this is the middle:
            - C calcifications
            - R raynaud's phenomena
            - E esophageal problem (dysphagia)

        - S syndactyli in fingers
        - T telangiectasia
- Nevus Flammerus
    - A "birthmark" characterized by being deep purple and flat
    - Composed of dilated capillaries
    - Usually on the head and neck
        - A special type is called the "port-wine stain"
        - May grow proportionally with the child
- Spider Telangiectasis
    - Focal, minute network of subQ arteries or arterioles
    - Arranged in a radial fashion about a central core
    - Located on upper body (face, neck upper chest)
    - Associated w/ hyperestrogenism (pregnancy, liver cirrhosis-chronic alcholics)
        - Disappears after delivery

Benign Neoplasms

- Hemangiomas—capillary type
    - Skin, subQ, oral cavity and lips
    - Liver, spleen and kidney
    - Strawberry-type found on infants grow rapidly in first few months
    - Begin to fade 1-3 years
    - 80% regress by 5 y/o
- Cavernous Hemangioma
    - Large cavernous vascular channels
    - Same locations as other, except sometimes seen in brain (can cause seizures)
    - *side effects of RADIOTHERAPY to the brain
- Glomus Tumors
    - PAINFUL, modified SMC tumors
    - Distal digits (under nails)
    - Arise from the glomus body—anastomizing arteries and veins in the pad of the nail which are used to REGULATE TEMPERATURE!

Malignant Neoplasms

    - Hemangiosarcome
    - Atypical (anaplastic) endothelial cells
    - Young w/ no gender predilection
    - Skin, liver (in industrial occupational dz from exposure w/ **polyvinyl chloride**), spleen, lungs, bones, and retroperitoneum
    - Associated w/ known carcinogens (polyvinyl chloride-liver)
- Karposi Sarcoma
    - Endothelial malignancy most commonly of the skin, but also mouth, GI tract, and respiratory tract)
    - Types
        - Classic (assoc. w/ old ppl in their legs—nothing to do with HIV)
        - European (chronic—assoc w/ HIV)
        - (HIV-neg) endemic
        - Immunosuppression or transplant-associated
        - AID associated (epidemic)
    - Pathogenesis
        - Viral association (KSHV—HHV8)
        - 

Tumors of the Heart (uncommon)

- Primary
  - Benign
    - Myxoma
      - The most common primary cardiac tumor in the ADULT. They are benign and found near the fossa ovalis in the LA in 90% of adults. They arise from endocardial mesenchymal cells, which proliferate and protrude into cardiac chambers. On microscopy, myxoma cells, endothelial cells, and SMC are found in mucopolysaccharride background. They may cause tumor emboli or ball-valve obstruction and syncopal epidsodes as they act on the MV
      - Myxoma→ can cause dizziness, loss of consciousness, problems w/ blood flow
      - Most common
      - In the atria
        - LA:RA Is 4:1
      - 10% have familial (Carney syndrome)
        - Carney sx: myxoma of the heart, endocrinopathies (endocrine glands), problems with the skin (lesions)
      - AUTOSOMAL DOMINANT
      - Skinmyxomas and hyperpigmentation
      - Cardiac myxomas
      - Endrinopathies—problems w/ endocrine glands
      - Mutation of some tumor suppressor gene
    - Lipoma
    - Rhabdomyoma (associated w/ tuberous sclerosis)
      - Most common primary cardiac tumor in CHILDREN
      - systemic dz w/ tumors on skin, in brain, in kidney and in heart. all benign. but can cause prob bc of locations.
        - on skin can be disfiguring bc usually on face
        - in brain cause seizure
        - in kidney can mimic glomerular dz w/ blood in urine
        - in heart can cause problem of blood flow
      - tuberous sclerosis
        - Autosomal dominant disorder dz in children that menifests w/ cortical tubers, hamartomas, hypopigmented “ash-leaf” skin lesions, renal angiomyolipomas and cardiac rhabdomyomas.
        - skin->face->disfiguring
        - brain->seizure
        - kidney-> hematuria
        - heart-> blood flow problems
      - On autopsy:
        - large firm, white tumor mass was found filling much of the left ventricle. This is a cardiac rhabdomyoma.
  - Malignant
    - Antiosarcome
- Most wil be Metastatic

Cardiovascular Effects of Noncardiac Neoplasms

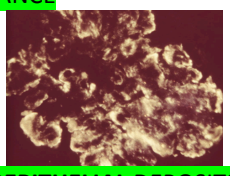
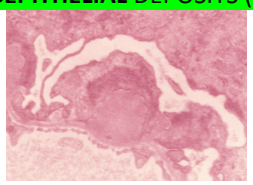
- Direct consequences of Tumor
  - Pericardial and myocardial metastases
  - Large vessel obstruction
  - Pulmonary tumor emboli
- Indirect Consequences of Tumor (complications of circulating mediators)
  - Nonbacterial thrombotic endocarditis
  - Carcinoid heart disease (right)
  - Pheochromocytoma-associated heart disease
  - Myeloma-associated amyloidosis
  - **Know trousseau sign of malignancy (marantic endocarditis)
- Effects of Tumor Therapy
  - Chemotherapy

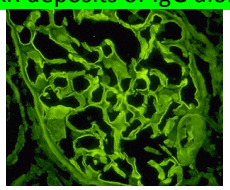
- Radiation Therapy

GLOMERULAR DISEASES

- Diagnosis of Glomerular Dz
  - Renal bx
  - LM w/ special stains
    - Periodic Acid Schiff→ mesangium
    - Jones/silver→ BM
      - Nephrotic Sx
    - Trichome→stains collagen→ Fibrosis
      - Chronic renal failure
  - Immunofluorescence
    - What deposits are made of
      - If C3 and C4 then classic pathway
      - If just C3 then alternative pathway
    - Where deposits are
  - EM
    - Where deposits are
- Mesangium
  - Cells
    - Contractile—regulate BF (act like SMC)
    - Phagocytes—can cause inflammation and phagocytose
  - Matrix
    - Support for glomerulus
- Proteinuria
  - 1+ = <500mg/ 24 hours
  - 2+= <1000mg/24 hours
  - 3+= 2 grams in 24 hours
  - 4+ (nephrotic range)= >3.5g /24 hours
- Fixed Tissue Antigens
  - in the kidney there are fixed to the BM made of collagen type IV
  - Glomerular injury due to antibodies to antigen fixed on the BM → antigen is non collagen α 3 chain of type IV collagen.
    - Only dz that fits this is GOOD PASTURES SYNDROME = ANTI GLOMERULAR BM DZ
- Immune Complex Nephritis
  - Type 3 hypersensitivity
    - Granular deposits of IgG-Ag complement immune complexes consider:
      - Poststrep
      - Type II RPGN
      - Membraneous glomerulopathy
  - Antigen + Ab→ IC circulating → they deposit in BM and activate **classic** complement → PMN's are attracted and release lysosomal enzymes→ tissue damage→ GLOMERULONEPHRITIS/POST STREP
  - If There is activation of alternative pathway of complement → results in cleave of C3 so you bypass C1, 2, and 4 → PMN enyzmes and lytic effect of complement → tissue damage→ MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS (MPGN)
- **NEPHRITIC**
  - Etiology
    - Proliferation of mesangial cells and necrosis
    - Pathology of this condition is the result of inflammation of the glomerulus and neutrophil-related injury
  - Symptoms
    - Hematuria
      - Secondary to destruction of glomerular capillaries and loss of RBC's into bowman space→ dysmorphic RBC and RBC casts of U/A
    - RBC casts
    - Mild Proteinuria
      - may be observed as a result of the glomerular capillary injury
    - HTN

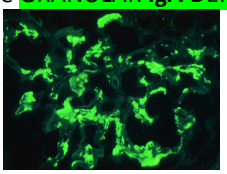
- Secondary to ↑ fluid retention by the kidney due to ↓ GFR.
- Oliguria
  - Secondary to glomerular injury as a result of infiltration of inflammatory cells and IC deposition→ obstruction of glomerular capillary lumen→ ↓ GFR → oliguria and azotemia
- Azotemia
  - ↑ in BUN and Creatinine

- DISEASES
  - Acute proliferative glomerulonephritis (post strep/infections)
    - Most frequently develops following an infection w/ certain strains of GABHS
    - Pathogenesis is secondary to IC deposition in the glomerulus w/ resulting complement activation and inflammation
    - Presentation
      - Usually children btwn 2-6 but sometimes in adults
      - ~10 days post pharyngeal infection (SORE THROAT) or 2-3 weeks after skin infection (IMPETIGO) w/ GABHS
      - Hematuria, HTN, azotemia
    - Dx
      - Serum
        - ASO titer
        - C3 and C4 low –classical pathway
        - ↑ BUN/Cr
      - U/A
        - Smoky brown colored urine
        - RBC and **RBC casts**
      - Renal bx
        - LM: Hypercellular and enlarged glomeruli (mesangial cell proliferation)
        - IF: IGG and C3/C4 **COARSE GRNAULAR** DEPOSITS w/ LUMPY-BUMPY APPEARANCE
          - 
        - EM: **SUBEPITHELIAL** DEPOSITS (**HUMPS**)
          - 
    - Prognosis
      - Excellent in kids (90% resolve)
      - A little worse in adults (70% resolve)
  - Rapidly progressive glomerulonephritis (RPGN, crescentic)
    - Proliferation of the parietal epithelial lining of Bowman capsule (forms a crescent)
    - More common in adults (30-60) and slightly more common in MEN
    - Presentation
      - Types
        - I: Goodpasture sx
          - IF: ANCA negative, LINEAR IGG and C3 along GBM
        - II: Poststrep GN, SLE, IgA nephropathy, HS Purpura
          - IF: ANCA negative, granular LUMPY BUMP deposits
        - III: Wegener granulomatosis or idiopathic
          - IF: cANCA-Postive!, no deposits on GBM
    - Dx
      - Serum
        - BUN/Cr may rise rapidly
        - Anti-GBM Ab—goodpasture sx
        - cANCA +→ Wegener

        - ↓ complement in some
    - U/A
        - RBC, proteins, WBC, casts!
    - Renal Bx
        - LM: CRESCENT FORMATION –consist of proliferated glomerular parietal cells; Bowman space is filled w/ monocytes and macros. Large amts of fibrin accumulate w/in the cellular layers of the crescents.
- Anti-GBM dz—GOODPASTURE SX
    - Abs against GBM. Symptoms can be isolated to the kindey or may be seen in lung b/c cross reactivity of antigens (α3 chain of type IV collagen) that are common to both alveoli and GBM
    - Underlying pathogenesis is related to HYPERSENSITIVITY TYPE II
    - Presentation
        - Possibly after having an URTI
        - **HEMOPTYSIS AND HEMATURIA**
        - Hematuria and other nephritic sx
        - Rapidly progressive
        - Pulmonary hemorrhage → hemoptysis and dyspnea
            - If it is idiopathic anti-GBM dz→ only kidney involved no lung
    - Dx:
        - Serum
            - Anti-GBM abs
            - C3 normal
            - CBC: slightly anemic maybe
        - U/A
            - RBC, RBC casts, mild proteinuria
        - Renal bx
            - LM: cellular accumulation in bowman space and CRESCENT FORMATION (leakage of **fibrin** in bowman's space and the **parietal cells** around bowman's capsule proliferate)
            - IF: LINEAR deposits of IgG along the GBM
            - 
    - Prognosis
        - w/o tx→ ESRD w/in 1 year
- Wegener Granulomatosis
    - Systemic dz that presents as focal necrotizing vasculitis and necrotizing granulomas in both URT and LRT (lungs) in association w/ necrotizing glomerulonephritis
    - Presentation
        - **HEMOPTYSIS AND HEMATURIA**
        - Nonspecific sx
        - **Sinus/Nose, Lung** and kidney involvement!
            - Chronic sinusitis, hemoptysis , and hematuria
        - THINK C's
            - C-ANCA
            - CORTICOSTEROID
            - CYCLOPHOSPHAMIDE
    - Dx
        - Serum
            - C-ANCA POSITIVE
            - Complement normal
        - Renal Bx
            - LM: Focal Necroitizing w/ CRESCENTS
            - IF: Variable
            - EM: Necrosis
- Polyartritis Nodosum

- Characterized by inflammation of small and medium sized arteries and typically affects the vessels of skin, peripheral nerves, kidneys, joints and GI tract.
- Histologically finding involve a transmural necrotizing inflammation of small and med sized arteries which can leak to arterial wall weakening, luminal obstruction and aneurysm formation w/ resultant downstream ischemic damage
- Presentation
    - Major Systems involved: RENAL, GI, MUSCULOSKELETAL, CNS, SKIN
    - Primarily 40-60 years odl
    - More common in **MALE**
    - Skin lesions (palpable rash, tender nodular lesions, infarcts of fingertips)
    - FEVER
    - NO LUNG
    - Peripheral neuropathy
    - HTN w/ renal sediment abnormalities
    - ORCHITIS (SWELLING OF TESTICLES)
- Dx
    - Serum
        - ↑ ESR
        - normocytic anemia
        - ↓ complement
        - ASSOCIATED W/ HEP B (30%)
        - CBC—EOSINOPHILIA
        - p-ANCA + in small % of pts
    - U/A
        - RBC, RBC casts, 1+ protein
    - Vessel bx
        - Segmental Large and Medium sized glomerular lesions
    -

- Hemolytic-Uremic Syndrome (HUS)
    - Young child has hematuria and bloody diarrhea for two days following eating ground beef (caused by E. coli 0157 toxin causes this dz)
    - Presentation
        - Kids <1
        - Preceding illness: 70-90% following gastroenteritis, 15% following URTI, Postpartum (6 wks after labor)
        - Oliguria
        - Renal failure
        - Hemolytic anemia
        - Thrombocytopenia
        - E. coli 0157 Toxins
    - Pathogenesis
        - Intravascular coagulation (↓ platelets and ↑ Fibrin split products)
    - Dx:
        - Serum
            - Normocytic anemia
            - BUN and Cr ↑
            - ↓ platelets
            - ↑ FSP
            - Shistocytes on peripheral smear
                - Other reason to see schistocytes→ TTP, Microangiopathic hemolytic anemia (MAHA), Thrombocytopenia, renal failure, DIC (MAHA and renal failure), Malignany HTN and scleroderma (MAHA)
            -
- Membranoproliferative glomerulonephritis (MPGN)—either nephritic or nephrotic
    - See nephrotic
- IgA nephropathy (Berger)
    - More common in CHILDREN and YOUNG ADULTS

- Suspected to arise in individuals w/ an abnormality in IgA production and clearance leading to deposits of IgA in the mesangial matrix which leads to glomerular injury and nephritic sx
- MOST COMMON GLOMERULOPATHY/HEMATURIA WORLDWIDE
- Very similar to Henoch-Schonlein purpura (except this is a vasculitis w/ IgA nephropathy as a component of the dz)
- Presentation
  - Hematuria ~1-2 days after URTI or GI infection
  - Hematuria lasts for several days then resolves and reoccurs every few months
- Dx
  - Serum
    - C3 normal
  - U/A
    - Painless spontaneous hematuria (gross and microscopic)
  - Renal bx
    - LM: variable
    - IF: diffuse GRANULAR **IgA** DEPOSTIS w/ specific distribution to mesangial cells
    - 
- Tx
  - Steroids
- Prognosise
  - Kids: benign
  - Adults: 19% go into Renal failure and 32% have chronic HTN
  - RECURRENCE IN RENAL ALLOGRAFTS

- Henoch-Schonlein Purpura
  - Actually a small vessel vasculitis that is characterized by PALPABLE RASH, colicky abdominal pain, arthritis, and hematuria
  - Thought to be caused by IgA, C3 and IC deposition in arterioles, venules and capillaries.
  - Presentation
    - More common in FEMALES < 7
    - More common in MALE > 8
    - Involves **skin** (rash), CT, joints (**arthralgia**), kidneys (**hematuria**), GI (**abdominal pain/blood in stool**) and the scrotum
      - Usually after GI and Cutaneous manfiestations
    - Most common in younger kids and in males
    - H/o **URTI ~50%**
    - PALAPABLE RASH On lower extremities
    - Testicular swelling and maybe a h/o bloody stools
  - Dx
    - U/A
      - RBC and RBC casts—gross and microscopic
    - Serum
      - BUN and Cr ↑
      - Serum IgA ↑
      - Normal Platelet count
      - Normal Bleeding Time
    - Renal Bx
      - Will look JUST LIKE BERGER DISEASE—IgA deposits all over mesangium!!! But NO lumpy bumpy appearance on IF
      - LM: Proliferatoin (focal or diffuse), necrosis, and crescents
      - IF: IgA, IgG, C3 Mesangial deposits and IgA deposits in SKIN

- Hereditary nephritis (Alport Dz)
  - Hereditary forma of glomerular injury that is X-LINKED RECESSIVE caused by an error in the synthesis of α5 CHAIN OF TYPE IV COLLAGEN (major component of the GBM and defects lead to

renal dysfunction). This type of collagen is found elsewhere in the body so pts may also have NERVE DEAFNESS, LENS DISLOCATION, and EARLY DEVELOPMENT OF CATARACTS

- Presentation
  - 5-20 y/o
  - Initially asx
  - Later have damage→ ↓ GFR→ ESRD
- Dx
  - Serum
    - C3 normal
  - U/A
    - Gross hematuria, mild proteinuria
  - Renal bx
    - LM: Glomerular and mesangial proliferation
      - FOAM CELLS (interstitial cells w/ accumulation of lipids)
    - EM: SPLITTING OF THE LAMINA DENSA

- Lupus nephritis—either nephritic of nephrotic
  - See nephrotic

- **NEPHROTIC**
  - Etiology
    - Results from an increased permeability of the GBM (leaky) secondary to cytokines released by macrophages→ these cytokines induce fusion of podocytes and obliterate the negative charge of the GBM→ loss of protein in the urine (esp LMW, negative charged ones like albumin)
  - Familial Nephrotic Sx
    - Mutations in Nephrin (transmembrane glycoprotein in the slit diaphragm between adj foot processes) and podocin leaking to a leaky GBM
      - Nephrin molecules from adjacent podocytes bind to eachother through disulfide bridges at the center of the slit diaphragm
      - Podocin—also crucial role in maintaining selective permeability of the Glomerular filtration barrier
  - Symptoms
    - **Proteinuria** (>3g/24 hrs)
      - Membranes are thicker but mutations in Nephrin and podocin make BM leaky
      - also changes in electric charge of the BM regardless of how thick or thin they are
    - **Hypoalbuminemia**
      - Lost in urine → ↓ serum oncotic pressure → edema
    - **Edema**→ loss of fluid in the circulation → activation of RAAS, ↑ SNS, release of AVP/ADH, and ↓ ANP release → → → increase renal electrolyte and water retention → worsening edema
    - **Hyperlipidemia**
      - b/c ↑ production of lipoproteins by the liver in an attempt to maintain the falling oncotic pressure
      - and hypoalbuminemia triggers an ↑ in cholesterol in the liver through a poorly understood mechanism
    - **urinary fatty casts (OVAL FAT BODIES)**
      - **Maltese-cross configuration due to presence of cholesterol (when viewed under polarized light)**
      - **Lipid droplets w/in tubular cells**
    - **Hypercoagulation**
      - b/c loss of antithrombin III through damaged glomeruli→ ↑ risk for renal vein thrombosis
    - *patient w/ nephrotic sx are at high risk for infections w/ encapsulated bacteria like staph and pneumococci due to loss of gamma globulins in the urine
  - DISEASES
    - Minimal change dz/ Lipoid Nephrosis/Nil Disease
      - Most frequent cause of nephrotic sx in MALE CHILDREN and equal male:female during adulthood
      - It is named b/c of the normal appearance of the glomeruli under LM
      - EM, however, shows fusion (effacement) of visceral epithelial foot processes, thereby causing ↑ glomerular permeability
        - Pathogenesis: T-cell derived factors→ causing podocyte damage and effacement
      - Often preceded by respiratory infection or routine immunizations

- PCT are often heavily laden w/ lipids secondary to ↑ tubular reabs of lipoproteins that passed through the injured glomerulus→ so this dz is AKA LIPOID NEPHROSIS (cell mediated immune injury—cytotoxic antibodies—injury to the foot processes of the glomerulus)
- Presentation
  - Kids 2-3
  - Insidious (SLOW) onset w/o any obvious clinical cause
  - **SELECTIVE PROTEINURIA—primarily albumin is lost**
  - **Edema**
  - Renal function is maintained w/ maybe a SLIGHT ↓ in GFR
- Diagnosis
  - See signs of nephrotic sx along with EM finding
  - Renal bx (usually don't renal bx tho they usually just give empiric steroids)
    - LM—no obv changes. Maybe lipoid appearance of cells in PCT (lipoid nephrosis)
    - EM—**EFFACEMENT/FUSION of visceral epithelial foot processes and ↑ lipoprotein in PCT**
- Tx:
  - Predisone (oral glucocorticoids)
- Prognosis: good in kids (>90%) and worse in adults (~50%)

- Focal segmental glomerulosclerosis (FSGS)
  - Fibrosis of only a segment of the affected glomeruli
  - More severe form of minimal change dz due to the similar fusion of visceral epithelial foot processes.
  - The pathologic lesion is sclerosis of <50% of the glomeruli (**focal)** w/ the sclerosis involving only distinct portions of the affected glomeruli (**segmental)**.
  - 33% of nephrotic sx in adults and 50% of nephrotic sx in African Americans
  - Also is the most common glomerular dz in **HIV patients**
    - Glomeruli may appear collapsing so is known as **COLLAPSING FSGS**
  - Kids w/ this will have nonselective proteinuria and have a higher incidience of hematuria and HTN than w/ minimal change dz
  - Presentation
    - Nephrotic sx (60-80%)
    - Nonselective proteinuria –4+
    - HTN (25%)
    - Azotemia (30%)
    - Mild hematuria
    - Maybe ↓ Renal fx
    - Types
      - C1Q (Seronegative Lupus)
      - Collapsing FSGS
        - Assoc. w/ HIV and heroine use
  - Dx
    - Renal bx
      - LM- **FOCAL** accumulation of hyaline material (see w/ TRICHROME STAIN—collagen) and **SEGMENTAL** sclerosis
        - Juxtamedullar glomeruli foxal sclerosis which SPREAD SUPERFICIALLY AS THE DZ PROGRESSES
          - importance of this means that if you think your pt has this you cant do a superficial bx of the kidney bc early on nothing will show up…need to do a deep core bx
      - IF: Large focal segmental IgM (so large it gets stuck!) in the mesangium
  - Tx
    - No response to steroids!
  - Prognosis
    - Poor w/ ~50% developing end stage renal dz w/in 10 years.
    - Even following RENAL TRANSPLANTATION HIGH RISK OF REOCCURENCE
- Diffuse Membraneous glomerulopathy/ Membraneous Glomerulonephritis
  - Thick GBM but no proliferation
  - Possibly IC deposition which is supported by its association w/ certain infections and systemic dz

- **LEADING CAUSE OF NEPHROTIC SX IN ADULTS (30-50 y/o) and PREDOMINANTLY IN MEN**
- Presentation
    - Insidious (SLOW) onset of nephrotic sx
        - CHRONIC IC DZ
            - slow and indolent course. Complement activation is slow and mild but b/c its chronic then serum complement is normal
    - NONSELECTIVE PROTEINURIA in otherwise healthy pts
    - Associated w/
        - SLE
        - RA
        - Infections like Hep B and C
            - Hep B assoc. also seen in PAN
        - Poison Ivy
        - Syphilis
        - Schistosomiasis
        - Malaria
        - Leprosy
        - Drugs—gold and penicillamine
        - Malignancy
            - Lymphoma, GI carcinomas
        - Renal Vein Thrombosis
            - Pt arrives in ER and complains of SEVERE one sided flank pain and no stones and you do imaging and testing and you see they have a clot in the renal vein. If you check the urine of this pt they will have nephrotic levels of protein in their urine
- Dx
    - U/A
        - 4+ protein
    - Renal bx
        - LM: **diffuse GBM thickening** due to **SUBEPITHELIAL DEPOSITS** nestled against the GBM
        - EM: Subepithelial deposits in a SPIKE (extensions of the GBM around the deposits) and DOME (deposits in the GBM) pattern
            - IF: FINE GRANULAR IgG and C3
            - 4 stages
                - 1. Epimembraneous deposits
                - 2. Intramembraneous Deposits and Spikes—deposits btwn the spikes
                - 3. Intramembraneous Deposits w/in BM
                - 4. Radiolcent areas (where deposits used to be)

- MPGN
    - Thick GBM w/ hypercellular glomeruli
    - Can occur idiopathically or secondary to monoclonal immunoglobulin deposition dz's, autoimmune dz (SLE), chronic thrombotic microangiopathies, or chronic infections
    - Types
        - Type I (2/3rd of cases)—MESANGOCAPILLARY
            - Slow Course
            - Deposition of IC's
                - So C3 and C4 involved
            - Associated w/ HEP B, HEP C, and CRYOGLOBULINEMIA
            - Some cases have NEPHRITIC presentation
            - More common in FEMALES
        - Type II (1/3rd of cases)—DENSE DEPOSIT DZ
            - Seen teens, no sex predilection
            - Usually seen after an infectious Dz (namely strep and pneumonia)
            - Assoc. w/ C3 nephritic factor (C3NeF)←an IgG autoantibody
                - Alternative Complement pathway
                    - So ↓ C3 but normal C4 and only C3 deposits

        - AKA DENSE DEPOSIT DZ—due to the deposition of an **electron dense material between the lamina densa and subendothelial space of the GBM**
        - C3 present in deposits but **NO IGG deposits**
    - Type III—Mesangial Proliferative
- Presentation
    - Normocytic anemia
        - hemolytic, BM failure, BM replacement, chronic dz (this is where this one fits here cuz she has chronic renal dz), acute blood loss
    - ↑ Cr
    - U/A
        - 2+ blood
        - 4+ protein
        - RBC casts
        - Oval fat Bodies
    - Type I—usually nephrotic but can be either. Familial
        - Low C3/4
        - LM: Lobular Pattern of proliferation of mesangial cells, ↑ mesangial matrix, thickening of BM. SILVER STAIN—SPLIT BM
        - IF: C3/4 DEPOSITS IN PERIPHERAL LOBULAR DISTRIBUTION
        - EM: MEANGIALIZATION → mesangial cells w/in the BM (gives the split appearance)
    - Type II—either nephrotic or nephritic presentation or a mix of the two
        - ↓ C3
        - IF: DISCONTINOUS LINEAR DEPOSITS OF C3
        - EM: RIBBON-LIKE DEPOSITS IN LAMINA DENSA
- Dx
    - Renal bx
        - Thickening of GBM and proliferation of mesangial cells
        - EM: GBM appears to be divided by an electron dense material
            - Type 1: SUBENDOTHELIAL deposits of IGG and C3 **(HUMPS)**
                - Ingrowth of the mesangium splits the GBM, creating a tram-track appearance
            - Type II: INTRAMEMBRANEOUS depsoits and ↑ size of glomeruli
                - Also see tram-track appearance in the capillary wall as a result of the GBM thickening
- Prognosis
    - Type I: benign course
    - Type II: worse prognosis w/ gradually deteriorating GFR→ ESRD after 5-10 years
    - RECURS IN RENAL ALLOGRAFT

- Diabetic nephropathy assoc w/ systemic dz
    - Leading cause of ESRD in western world
    - First sign of injury to the glomerulus = **MICROALBUMINURIA (**happens ~5-10 years before other sx develop).
    - More common in Type I DM than DM-2
    - Presentation
        - HTN
        - Edema (result of fluid retention)
        - Arteriosclerosis of renal artery and efferent arterioles
        - If untx: nephrotic range of proteinuria
    - Dx
        - Suspect esp in pts w/ DM1 or 2 that have result of end organ damage already (retinopathy, neuropathy, positive dipstick proteinuria)
        - LM: Thickening of GBM and expansion of the mesangium
            - Nodular Sclerosis
                - Kimmelstiel-Wilson lesion (areas of nodular glomerulosclorsis) is seen
            - HYALINIZATION OF AFFERENT AND EFFERENT ARTERIOLES
            - HYALINE DROPLETS
                - Fibrin Cap in BM

- Capsular drops in Bowman's capsule
- EM: Microangiopathy

- Renal amyloidosis associated w/ systemic dz
  - Characterized by deposition of fibrous, insoluble proteins in a β-leated sheet conformation in the Extracellular space of organs (renal glomeruli)
  - It is a multisystem disorder of protein folding
  - Familial
    - Seen in younger pts
  - Secondary
    - Older patients (40's)
  - Primary
    - Pts in their 60's
  - Two Types
    - Amyloid L (AL)
      - Derived from Ig light chains (Bence Jones protein in the blood or urine is associated w/ multiple myeloma)
    - Amyloid A (AA)
      - Associated w/ chronic inflammation (RA, Tb)
  - When Ig's light chains lacking the β-pleated configuration deposit in the kidney the disease is called LIGHT CHAIN DEPOSITION DISEASE
  - Presentation
    - Slow course
    - Signs and symptoms of primary dz if the amyloidosis is secondary
    - Nephrotic range proteinuria, severe edema and renal insufficiency
  - Dx
    - LM: Nodular Lesion! Tissue stained w/ CONGO RED has deposits of amyloid that show APPLE-GREEN BIREFRINGENCE under polarized light.
      - In addition mesangial expansion is present w/ amorphous hyaline material (amyloid) and thickening of GBM
        - amorphous pink depositis of amyloid may be found in and around arteries, in interstitium, or in glomeruli
    - IF: POSITIVE LIGHT CHAIN DEPOSITS (MOST LAMBDA)
    - EM: NON-branching fibrils in BM, masangium and vessel walls
  - Tx:
    - No response to steroids
- Lupus nephritis
  - Presentation
    - Dz of middle aged ppl
    - More common in FEMALES
    - During early SLE pts may not have sx of kidney dz but as the dz progresses, kidneys are almost uniformly affect, and patients present w/ either nephrotic or nephritic syndrome or both→ ESRRD ultimately
    - Most common sx
      - Weight gain
      - High BP
      - Darker FOAMY urine (lots of protein)
      - Swelling around the eyes, legs, ankles or fingers
  - Dx
    - ↑ ANA
      - low titer is anything <1-->512 and it depends where your starting point is. If you start at 1-32 then it is less than 1--512. If you start at 1-40 then it is less than 620
      - High titer ANA Is what is important here!. It has different patterns:
        - homogeneous --> where the entire nucleus lights up on IF and this indicates the presence of **anti-histone Ab's**. This pattern is usually seen in drug induced lupus. It is NOT ASSOC. with renal issues but may be associated w/ some skin issues

- peripheral--> rare but if we see it we can say for sure that the pt has **anti-ds DNA lupus**.
- nucleolar--> indicates **anti-RNA** which is seen in **scleroderma**
- SPECKLED--> most common. Has diff subcategories
    - ENA
        - RNP (ribonuclear protein)→ Mixed CT Disease (MCTD)—NO RENAL INVOLVEMENT
        - antiSmith→ SLE
    - SCL70→ **Scleroderma** (progressive systemic sclerosis (scars))
        - HTN (vessels fibrosed)
        - Pulmonary fibrosis
        - Raynaud's phenomenon
        - Renal Failure—kidney vessels are sclerosed
        - ANA: 1:20000 and speckled anti SCL70 is positive
        - Thin leathery skin on her hands and face why? B/c fibrosis of the dermis b/c all of her hair follicles, sweat glands and sebaceous glands are destroyed by the fibrosis so thats why skin it shiny and leathery
        - If you do a skin bx on a pt with SLE you will **see IgG and C3 deposits at the dermal epidermal junction in a granular pattern**
    - SSA (anti La) or SSB (anti-RO)→ Sjogren syndrome
    - Anti JO→ dermatomyositis
- ↑ Anti-DNA
- Serum
    - Low complement—this is an IC dz
- Renal bx
    - We only need to know type V
        - V- Membraneous nephritis –characterized by extremem edema and protein loss
    - Other
        - Focal proliferative segmental→ mild hematuria and proteinuria
        - Diffuse proliferative→ gross hematuria and moderate proteinuria and casts
        - Necrotizing form (VERY AGGRESSIVE)
            - Tubules→ necrosis
            - Interstitium→ inflammation
            - Vessels→ vasculitis
            - LM: Ig's and Complement deposits in MESANGIUM and TUBULES
                - IT DEPOSITS EVERYTHING IN THE GLOMERULUS→ **FULL HOUSE IF**
            - EM: SUBENDOTHELIAL DEPOSITS
- Tx
    - Steroids or Imuran
- Prognosis
    - Focal → no failure
    - Diffuse or necrotizing → renal failure

- **RECURS IN TRANSPLANT**
    - **FSGS**
    - **IgA NEPHROPATHY**
    - **MEMBRANOPROLIGERATIVE GN TYPE I**
- **NODULAR LESIONS**
    - **AMYLOID**
    - **DIABETES**
    - **LIGHT CHAIN NEPHROPATHY (WASN'T IN GLOMERULAR DZ LECTURE)**
- **LOW C3**
    - **POST STREP**

- **MPGN TYPE I AND II**
- **SLE**
- **CRYOGLOBULINEMIA—DIDN'T TALK ABOUT THIS (WILL SEE PT W/ RENAL DZ AND H/O HEP C)**

RENAL VASCULAR DISEASES

- Renin
  - Produced in the JG (afferent arteriole)
  - Proteolytic enzyme
    - Mainly formed and stored in the JG cells w/in the MD of the kidney
  - Synthesized from a larger precursor protein –Big RENIN
    - Big RENIN is converted into RENIN (active form) w/in the JG cells
  - Renin is released in response to:
    - ↓ in hydrostatic pressure (↓ MAP)
    - Hyponatremia (↓ Na)
    - Hyperkalemia (↑ K)
    - ↓ in catecholamines
    - ↓ in AT II
    - ↓ ANP (this happens when volume is low)
  - Renin has several isoenzymes that are regulated by cAMP
    - It acts on angiotensinogen and α2 globulin formed by the liver
  - Renin converts angiotensinogen → ATI → AT II by the enzyme ACE which is found in the pulmonary and vascular endothelium (it is also found in the cell membranes of the kidney, heart and brain)
  - ATII is a peptide responsible for:
    - The physiologic effect on the target tissues
    - VASOCONSTRICTION
    - Stimulates the release of ALDOSTERONE
    - Stimulates the release of catecholamines from the adrenals
    - Stimulates the release of NE from SNS
    - Stimulates release of AVP/ADH
    - ↑ distal tubular reabs of Na→ leads to water reabs→ ↑ BP
  - AT II is an octapeptide that is split into a heptapeptide (AT III)—which modules aldosterone secretion
  - Renin, through ATII directly **STIMULATES** the **SYNTHESIS** and **SECRETION** of aldosterone from the ZONA GLOMERULOSA of the adrenals
    - Zona glomerulosa--aldosterone
    - Zona fasiculata--corticosteroids
    - Zona reticularis--sex hormones
- Aldosterone
  - Acts at the mineralcorticoids receptor located in the cells' lining the collecting ducts of the kidney
    - It will cause changes in electrolytes→ ↑ Na reabs and ↓ K reabs
  - This leads to:
    - ↑ BV
    - Renal K loss
    - Stimulates genes for collagen synthesis
      - For TGF
      - For inflammatory factors
      - For plasminogen activator inhibitor type 1
  - The synthesis of aldosterone is restricted to the ZONA GLOMERULOSA (think glomerulus in the kidneys and aldosterone is in the kidneys)
    - Aldosterone synthesase converts corticosterone to aldosterone
    - The major stimuli for aldosterone secretion :
      - AT II
      - Hyperkalemia
      - A weaker stimulus is ACTH (pituitary gland)
    - Inhibitors of aldosterone synthesis are: (these things can be use to treat HTN when we have ↑ aldosterone)
      - Somatostatin (GH inhibiting Hormone)
      - DA

- Heparin
- ANP

RENIN and HTN

- Essential HTN can be classified based on renin levels
- HTN associated w/ ↑ levels of plasma renin
    - Renal parenchymal dz
        - ↑ Aldosterone production b/c renin stimulated ATII which stimulates aldosterone
        - ↑ hypervolemic retention of Na (and water)
        - ↑ K excretion
    - Renal vasculopathy
        - Major arterial lesions
        - Segmental lesions
    - Renin excreting tumors
        - Very RARE
        - Can be renal or extrarenal
        - Most common in the JG
    - Malignant HTN
        - can have this b/c of renal parenchyma dz and also can have it b/c of renal artery stenosis (renal vascular HTN)
            - If the malignant HTN is b/c of renal parenchyma dz--give pt ACE inhibitors
            - If the malignant HTN is b/c of renal vascular stenosis/dz then ACE inhibitors will not help and they actually result in further renal problems. In renal vasc. dz you need to stent the vasculature b/c pts wont respond antiHTN meds (intractable HTN)
        - Tx w/ ACEI normalizes the BP
        - This is in contrast w/ renovascular HTN where ACEI results in further deterioration of renal functions
    - In renal vascular Dz
        - So if you have renal HTN and you want to stent it or do surgery on it you can predict whether the pt will respond well to surgery or not by measuring the ration of renin in renal vein of the effected kidney (the one w/ stenosis) vs. the nonaffected side and if that ratio is 1.5:1 the surgery will improve the outcome!
        - Renin ratio of the renal vein in affected side/nonaffected side PREDICT the response to SURGERY
            - Ratio of 1.5:1→ surgery will improve the outcome
        - Peripheral renin levels are poor predictor of response to surgery b/c they vary a lot
    - In ESRD w/ intractable (not responding to meds)
        - HTN
        - Elevated renin
        - If these occur then Nephrectomy must be performed
    - Elevated Renin in transplant rejection indicated ischemic injury
    - Drugs
        - ↑ renin substrate activity
            - Contraceptives (estrogen-containing)
            - Glucocorticoids
            - Diuretics
            - AntiHTN
- HTN w/ Low renin levels (if you have ↑ aldosterone)
    - Primary excess of mineralcorticoids
        - Primary aldosteronism
        - Pseudoprimary (idiopathic) aldosteronism
        - Glucocorticoid-suppressible aldosteronism
        - 11-deoxycortocosterone excess
        - 18-hydroxy-11-deoxycortocosterone excess
        - Adrenal carcinoma
    - Secondary excess of Mineralocorticoids
        - Licorice ingestion
        - Excess Na intake
        - Hyporenin hypoaldosteronism
            - Long standing essential HTN
            - DM
- HTN w/ normal renin levels

- Types and causes of HTN
  - Essential HTN (90-95%)
  - Secondary HTN
    - Renal
      - Acute glomerulonephritis
      - Chronic renal dz
      - Polycystic Dz
      - Renal artery stenosis
      - Renal Vasculitis
      - Renin-producing tumors
    - Endocrine
      - Adrenocortical hyperfunction (Cushing sx, primary aldosteronism, congenital adrenal hyperplasia, licorice ingestion)
      - Exogenous hormones (glucocorticoids, estrogen (including pregnancy-induced and oral contraceptives), sympathomimetics and tyramine-containing foods, MAO inhibitors)
      - Pheochromocytoma
      - Acromegaly
      - Hypothyroidism (myxedema)
      - Hyperthyroidism (thyrotoxicosis)
      - Pregnancy-induced
    - Cardiovascular
      - Coarctation of aorta
      - PAN
      - ↑ BV
      - ↑ CO
      - Rigidity of the aorta
    - Neurologic
      - Psychogenic
      - ↑ intracranial pressure
      - Sleep apnea
      - Acute stress, including surgery

MORPHOLOGY OF HTN

- BENIGN HTN
  - Benign HTN
    - hyalinization
  - Benign Nephrosclerosis
    - Hyaline arteriosclerosis
    - Hyalinization of the glomeruli
    - Interstitial fibrosis
    - Tubular atrophy
- MALIGNANT HTN
  - Onion skinning/ hyperplastic
  - Will see schistocytes!
  - Leads to:
    - Fibrinoid necrosis arterioles
    - Hyperplastic arterioles
    - Hyperplastic arteriolitis
    - Necrotizing glomerulitis
- Renal Artery Stenosis
  - Goldblatt Experiment in 1934
    - Constriction of one renal artery in dogs results in HTN as a result of renin secretion by the JG cells
  - Cause
    - ↑ renin atheroma
    - Fibromuscular dysplasia
      - Renal artery stenosis is usually in young women w/ intractable HTN that does not respond to meds and usually have fibromuscular dysplasia of the renal artery on one side and less commonly they can have atheromas

TUBULAR & INTERSTITIAL DISEASES

TUBULAR DISEASES

- Acute Tubular Necrosis (Associations: MUDDY BROWN CASTS< RHADBOMYOLYSIS, CRUSH INJURY)
  - MOST COMMON and IMPORTANT cause of ACUTE RENAL FAILURE
  - With tubular necrosis the tubules have the capacity to regenerate so if you treat whatever caused the injury the patient will recover
  - Two major types (same clinical picture but different morphology)
    - Toxic
      - These lesions are USUALLY DIFFUSE IN THE PCT so you get loss of bruch borders and epithelial cells
    - Ischemic
      - The lesions are segmental and have skip areas and they effect different segments but mostly in the PCT and some in the loop of Henle
  - 3 Major Mechanisms
    - Failure of glomerular filtration due to alteration of blood flow (poor perfusion)←this is what happens most of the time
    - Destruction of the Tubular integrity w/ leakage of tubular fluid into the interstitium
      - Can have direct damage to the lining epithelium of the tubule and they become leaks and leak fluid into the interstitium and that can lead to obstruction of the tubules
    - Tubular obstruction by edema and casts
  - Clinical Picture
    - 1. Oliguria 10-12 days
      - water + salt overload + hyperkalemia are the problems
        - hyperkalemia can lead to arrhythmias in the heart
        - Hyperkalemia can also lead to metabolic acidosis (b/c the tubules are functioning) and this can cause Muscle weakness and bradycardia
        - What happens when you have oliguria? You retain electrolytes (Na and K) they are not going out which is causing electrolyte imbalance
      - U/A: TUBULAR CELL CASTS/ MUDDY BROWN CASTS, RBC
    - 2. Polyuria >10-12 days
      - Now the pt is losing a lot of electrolytes instead of retaining them
      - ↑ volume of urine and ↓ Na, K, and Cl b/c they are lost in urine
    - 3. RECOVERY 17th day due to regeneration
      - Tubules gain back their concentrating ability
  - Complications
    - CV
      - Congestion, HTN, arrhythmias
    - CNS
      - Lethargy
      - Somnolence
      - Twitching
      - seizure (b/c of electrolyte imbalance)
  - Etiology
    - Toxic (DAMAGE IS MOSTLY IN THE PCT)
      - Heavy metals (mercury, lead, gold, arsenic)
      - Organic solvents (chloroform, carbon tetrachloride)
      - Antibacterial (polymixin, neomycin, sulfa)
        - When you give certain antibiotics you have to keep an eye on the BUN/Cr levels of your pt b/c you have to adjust doses according
      - Mushrooms
      - Pesticides
      - Ethylene glycol (antifreeze)
        - Antifreeze has a sweet taste so homeless ppl who cant buy alcohol drink this and get toxin ATN –tx is actually w/ ethanol
        - Characteristic finding is CALCIUM OXYLATE CRYSTALS IN THE URINE
      - **Gross appearance**
        - Pale swollen kidney b/c of edema

- **Microscopic Appearance**
  - Will see damage in the PCT→ loss of brush border and cells but INTACT tubular BM
  - The necrosis is quite obvious and is associated w/ INTACT BM
- Ischemic ATN
  - Cardiogenic shock, massive MI, hypotension, hypovolemic chock, gram – septic shock→ ischemia of the kidney→ ischemic ATN
  - FOCAL at MUTIPLE POINT w/ SKIP AREAS in between RUPTURE OF BM (tubulorhesis)
  - Occlusion of lumen by tubular casts/muddy brown casts
  - Affects both PCT and DCT
  - Causes
    - Renal vasoconstriction
      - Dehydration
      - Hypovolemic shock
      - Typical clinical manifestation are
        - Mismatched blood transfusion w/ massive hemolysis
        - Crush injury
        - Burns causing hemolysis
        - Septicemia caused by gram – bacteria

- INTERSTITIAL NEPHRITIS (TOXIC)
  - Acute
    - Can have sudden onset usually after antibiotic therapy (Methicillin) b/c of a type I hypersensitivity rxn→ renal failure and when you look at U/A will see EOSINOPHILS in urine and EOSINOPHILS in the blood and ↑ in IgE and possible evidence of UTI
  - Chronic
    - Aspirin (NSAIDS)
      - This is COX inhibitor so ↓ Prostaglandin synthesis→ PG ischemia→ ischemic damage of the kidney→ PAPILLARY NECROSIS + INTERSTITIAL LYMPHOCYTES
        - when the papillae necrosize you have tissue that needs to go out through the ureter and that causes severe pain (Like if you were trying to pass a stone) b/c ureter is contracting to get rid of necrotic tissue
          - papillary necrosis can be fata b/c it can lead to DIC
        - they will get interstitial lymphocytes b/c the Cox inhibitors can cause ischemia and direct toxicity eventually the kidney will be scarred
    - PHENACETIN (ANALGESIC)
      - → Direct toxic affect on the kidney→ papillary necrosis + interstitial lymphoyctes
    - In both will see PMN's in the urine but this isnt an infection so we call this STERILE PYURIA
- RENAL CHANGES IN MULTIPLE MYELOMA
  - Obstructive uropathy
    - Sticky/viscous light chain casts obstructing the tubules
  - Destruction of tubular integrity
    - b/c the light chain are stick and pluck out the tubular cells from the BM→ tubular cell damage
  - Amyloidosis
  - Interstitial Dz
    - Interstitial infiltration of plasma cells
  - LIGHT CHAIN GLOMERULONEPHRITIS
    - In MM we ar epsilling light chains in the urine and high high light chains in serum
    - Antibodies develop against these light chains→ IC dz→ deposition in the kidney→ activates complement
    - NODULAR LESIONS
  - Calcinosis
    - IN MM we have hypercalcemia→ this leads to metastatic calcification (high calcium is the cause)
      - *dystrophic calcification is due to calcium deposits on necrotic tissue

URINARY TRACT INFECTION

- UTI are second most common dz next to URTI
- Normally
  - Kidneys, Ureters and the Bladder are STERILE
  - Meatal portion of the Urethra and Perineum contain SAPROPHYTES and POTENTIAL PATHOGENS
    - the urethra and bladder are close to the perineum
    - so bacteria from the perineum can go to the urethra, once in the urethra and bladder the bacteria grow b/c urine is a very futile nutrient environment --> infection
      - Instrumentation (catheter) can cause this
    - Infection can then ascend to the bladder.
- Upper UTI is infections of the KIDNEYS (pyelonephritis)
- Most common UTI's are lower UTI's→ inflammation of the bladder and urethra
- Women are more likely to develop UTI's in their reproductive years
- Men develop UTI's when they are very old b/c their prostate becomes enlarged→ obstruction → ↑ risk for UTI
- Obstruction of Urinary tract leads to:
  - Residual urine b/c cant empty the bladder completely→ which leads to distention of the bladder so the bladder will need more blood and it wont get enough so → blood supply to the bladder is compromised → increases susceptibility to infection
- UTI occur through TWO routes
  - HEMATOGENOUS (RARE)
  - VESICOURETERAL REFLUX (COMMON)
    - This is the second most common cause next to diabetes
    - Urine flows back from the bladder to the ureter to the kidney B/c sphincter isn't strong enough in the bladder
    - Caused by:
      - Congenital abnormalities of implantation of the ureter in the bladder
      - Infection of Vesicoureteral junction (acquired)
    - Women w/ repeated UTI's → ↑ inflammation → scarring of the sphincter→ urine will flow back
- Organisms
  - E. Coli most COMMON
  - Other gram negative next common
  - Occasional—Enterococci and Staphylococci
- Normal Protective Mechanisms
  - The urethra acts as natural anatomic barrier
  - Mucosal IgA (secretory IgA)
  - Bactericidial substances (prostatic secretions in male)
  - So think about women----no bactericidal substances from prostatic secretions and shorter urethra= more UTI's than men
- Medulla of the Kidney
  - Is more vulnerable to infection WHY?
    - Low Blood supply
    - Hypertonicity of the medullary environment → ↓ phagocytosis
    - High concentration of Ammonia→ interferes w/ bactericidal actions of serum
- ACUTE PYLONEPHRITIS
  - Clinical picture
    - Systemic
      - Fever
      - Chills
      - Vomiting
    - Local
      - Urgency
      - Frequency
      - Dysuria
      - Back pain (b/c of infection in the kidneys)
      - B/c remember this is an ascending infection and bladder is also involved as well as the kindeys
    - Dx
      - U/A

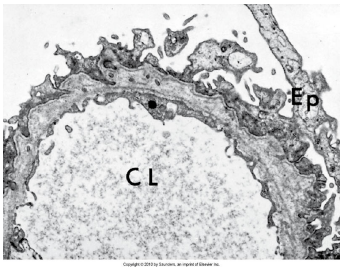
        - Bacteria
            - >10^6 microorganisms/mL of urine
            - use a calibrated loop and each colony = 100 bacteria
        - WBC CASTS→ RENAL INVOLVEMENT
        - RBC
        - ***wont see WBC casts if its cystitis or urethritis
    - Course
        - Acute pyelonephritis (if no obstruction) will heal and leave small scars
        - Can recur b/c of the reflux → more scarring → chronic pyelonephritis → papillary necrosis
    - **PAPILLARY NECROSIS**
        - IMPORTANT complication of pyelonephritis
        - Special hazard in patient w/ diabetes
        - CAN CAUSE DEATH
        - Morphology
            - Necrosis of the papillae→ sloughing of the papillary tips
        - REMEMBER—papillary necrosis also occurs w/
            - ANALGESIC ABUSE
            - SICKLE CELL DZ
            - DIABETES
            - ACUTE PYELO w/ OBSTRUCTION
            - **all of these cause ischemia which is why they are necrotizing
    - **STONE FORMATION**
        - Most stones are formed in the ABSENSE OF INFECTION and lead to INFECTION BY CAUSING OBSTRUCTION
        - Infection however can lead to stone formation namely w/ UREA SPLITTING ORGANISMS
            - Urea splitting organism: PROTEUS MIRABILIS
                - Splits urea into ammonia→ ↑ pH of urine (alkaline)→ PPT of Mg, Ammonium phosphate and calcium phosphate crystals→ can become large→ impact calyces→ STAGHORN STONE→ obstruction→ hydronephrosis→ stagnant urine → infection→ pyonephrosis
                    - Triple phosphate crystals are Mg, Ammonium, Calcium
                        - Magnesium ammonium phosphate= STRUVITE
                            - Formed in alkaline urine
                            - **Uric acid stones are formed in ACIDIC urine
                    - These crystals look like COFFINS/CASKET

- CHRONIC PYELONEPHRITIS
    - Result of recurring acute pyelonephritis
    - Gross
        - Multiple WEDGE-SHAPED scars on the surface of the kidneys
        - U-shaped geographic deep scares
    - Micro
        - Heavy interstitial lymphocytic infiltrates
        - Interstitial fibrosis
        - Arteriolar sclerosis
        - HYALINE CASTS IN TUBULES
            - Not specific for a type of dz they just tell you that you patient has a chronic renal problem
        - THRYOID LIKE ARRANGMENT OF TUBULES
            - b/c tubules are atrophic and they contain hyaline casts so under the microscope it looks like little thyroid-like follicles
        - Periglomerular fibrosis
        - Hyalinized glomeruli

CONGENITAL AND FAMILIAL RENAL DISEASES

- ANOMALIES OF DIFFERENTIATION
    - **1. SIMPLE CYSTS**
        - obstruction and impaired circulation
        - Rare in children, common in adults
    - **2. INFANTILE POLYCYSTIC DISEASE (POTTER I)**
        - Hyperplasia of interstitial portion of collecting tubules
        - bilateral symmetrical changes

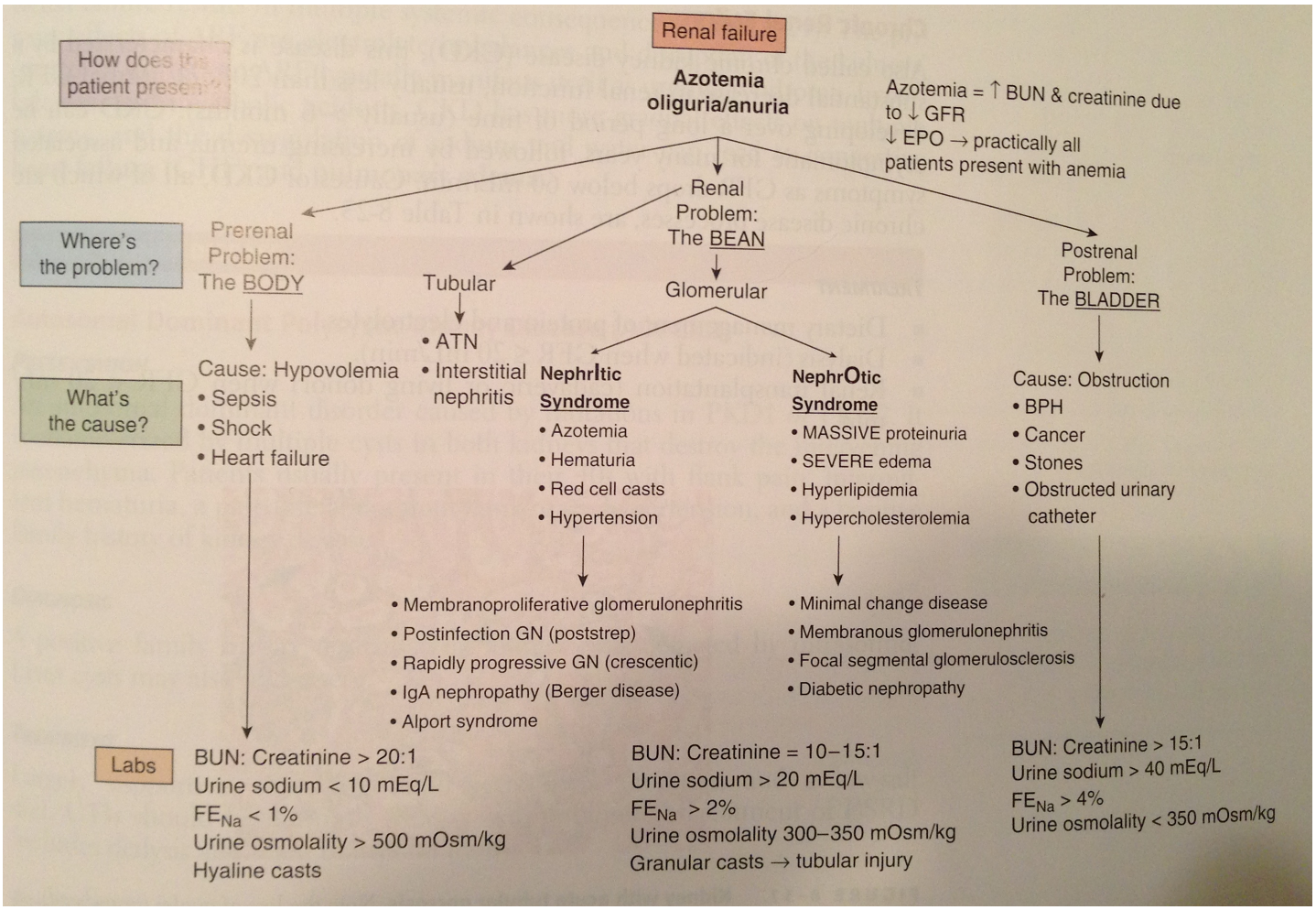
        - **radially** arranged cysts extending through cortex and medulla
            - these radially arranged cysts leave no room for any normal renal parenchyma to develop→ renal failure before they are born
        - Micro cuboidal or flat epithelium
        - AUTOSOMAL RECESSIVE
            - Mutation in PKHD1
        - liver and biliary ducts involved
        - Sometimes see PULMONARY HYPOPLASIA
        - INCOMPATIBLE WITH LIFE
        - THIS IS ASSOCIATED WITH OLIGOHYDRAMNION (DRY PREGNANCY)—very little amniotic fluid b/c the baby isn't putting out any urine
        - Mutation in $PKHD_1$ gene
            - Coding for a membrane-receptive protein→ Fibrocystin
    - **DYSPLASTIC KIDNEY (POTTER TYPE II)**
        - persistence of strtuctures inappropriate to the gestational age
        - cysts surrounded by undifferentiated mesenchymes including CARTILAGE
        - not hereditary, usually unilateral, can be segmental
        - If **bilateral**→ incompable with life
            - THIS IS ASSOCIATED WITH OLIGOHYDRAMNION (DRY PREGNANCY)
                - Also in Renal agenesis, dysplastic kidneys (this one), infantile cystic dz of the kidney
        - if **unilateral** usually associated with CNS abnormalities and esophageal atresia
    - **ADULT POLYCYSTIC KIDNEY (POTTER III)**
        - abnormality of interstitial an ampullary portions
        - AUTOSOMAL DOMINANT
            - Mutation in PKD 1 or 2
        - bilateral
        - 1/3 of patients have LIVER CYSTS
            - If they get too big must surgically remove (will get RUQ pain)
        - Cysts of pancreas also present
        - When these patients are born they have little cysts separated by normal renal tissue and as the person grows older the little cysts accumulate fluids (urine) and grow and over time they will grow and encroach on normal renal parenchyma
            - The stagnant urine/blood in these cysts → infections → stone formation
        - Also see renal failure and HTN in this
        - Gross:
            - bosselated large kidney
        - micro
            - cuboidal cells with brush borders
        - Clinically:
            - Hematuria
            - Hypertension
            - Usually presents later in life in fourth and fifth decades
            - Associated with BERRY ANEURYSM of cerebral vessels in 1/5 of patients (worst headache of a persons life)
                - Association w/ saccular aneurysms affecting the circle of Willis leading to a high incidence of subarachnoid hemorrhage
- MEDULLARY CYSTS
    - **SPONGE KIDNEY: MEDULLARY**
        - Cystic dilatation → communicate with collecting ducts and are bilateral
            - The renal tubules are in the medulla and when your tubules are not functioning you cannot reabsorb things → lose a lot of salt in the urine and eventual chronic renal failure
        - Gross: cysts in papillae
        - Micro: tall columnar
            - Renal cortex normal
        - Clinical: asymptomatic or stones plus infection
        - Pathogenesis UNKNOWN
    - **ADULT ONSET MEDULLARY CYSTIC DISEASE**
        - AUTOSOMAL DOMINANT

        - corticomedullary cysts
        - shrunken kidneys
        - salt loosing polyuria
        - chronic renal failure beginning in adulthood
    - **FAMILIAL JUVENILE NEPHRONOPHTHSIS**
        - AUTOSOMAL RECESSIVE
        - Corticomedullary cysts w/ shrunken kidneys
        - Salt wasting polyuria
        - Growth retardation
        - Anemia
        - Progressive renal failure beginning in childhood
- **HORSESHOE KIDNEY**
    - Failure of rotation and Inferior polar fusion Or Superior polar fusion
    - Clinical
        - The fusion piece in the middle of both kidney's can cause obstruction→ urine stagnation→ infection→ stones
        - Can be mistaken for tumor of the pelvis ir you don't know patient has this
- FAMILIAL GLOMERULAR DISEASES
    - **BENIGN RECURRENT HEMATURIA**
        - Sporadic or familial
        - Clinical Picture: recurrent microscopic or gross hematuria
        - Pathogenesis unknown
        - Morphology
            - LM no changes
            - IF– negative
            - EM - thin capillary loops
        - Prognosis good
        - To differentiate this from IgA Nephropathy do renal bx
    - **ALPORT SYNDROME**
        - Clinical picture
            - Female
                - Hematuria
                - Mild proteinuria
            - Male
                - Renal failure
        - Familial dz
            - **X-linked** and autosomal
            - Will see OCULAR and HEARING Defects
        - pathogenesis
            - abnormal α_5 chain of type iv collagen in the X-LINKED TYPE
            - abnormal α_3 and α_4 chain of type iv collagen in the AUTOSOMAL TYPE
        - Morphology
            - Light microscopy
                - Large number of **foamy histocytes** in interstitium
                - glomerular changes variable
            - IF – non-diagnostic
            - EM – characteristic lamellation/fragmentation of the lamina densa
                - Sometimes called moth eaten appearance
                - 

RENAL FAILURE

- Many conditions lead to either acute Renal failure (ARF) or chronic renal failure (CRF)
- 3 main categories of renal failure
    - Prerenal
        - Urine Osm >500
        - Urine Na <10
        - FE_{Na} (fractional excretion) <1%
        - BUN/Cr ratio >20
    - Renal
        - Urine Osm <350
        - Urine Na >20
        - FE_{Na} >2%
        - BUN/Cr ratio <15
    - Postrenal
        - Urine Osm <350
        - Urine Na >40
        - FE_{Na} >4%
        - BUN/Cr ratio >15
- Acute Renal Failure (ARF)
    - Abrupt onset ↓ in renal function as measured by GFR→ ↓ ability to maintain serum electrolytes and excrete nitrogenous waste
- Functions of the Kidney
    - Filtration
    - Reabsorbtion
    - Acid-base balance
    - Endocrine Function
- Metabolic changes in Chronic Renal Failure
    - Azotemia ↑ BUN and creatinine
    - Retention of Na and water
    - Hyperkalemia
    - Acidosis
        - Metabolic acidosis (High anion gap b/c anion gap = Na + K – Cl + Bicarb and Na and K are retained and bicarb is very low.
    - Hyperphosphatemia, hypocalcemia→ PTH→mobilization of calcium from bone
- AZOTEMIA
    - Elevation of BUN and creatinine indicates decreased nephron capacity b/c they are both cleared through the kidney
- ELECTROLYTE IMBALANCE (b/c of tubular damage)
    - Na+
        - 70% reabsorbed in proximal tubules via Na+-K+ transporter
            - Osmotic charge neutral process
        - 25% Reabsorbed actively in the ascending loop of Henle
            - Via Na+-K+- and cl- cotransporters
        - Further reabsorption occurs in the distal tubules
            - Distal reabsorption enhanced by the action of the renin-angiotensin-aldosterone axis
    - Water
        - Water retention at the collecting ducts is effected by increases in ADH
            - When we have problems w/ Na retention we retain water also
        - In renal failure there is retention of Both Na+ and water which will ↑ BP
    - K+
        - Potassium excretion also impaired in renal function

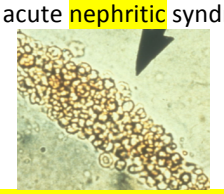
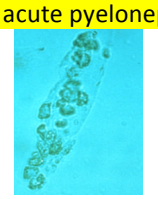
        - Resulting in hyperkalemia → which can lead to cardiac arrhythmia
- ACIDOSIS
    - Tubular damage = impaired secretion of ammonium
    - This results in impaired hydrogen ion reabsorption
    - This results in metabolic acidosis
        - ↑ anion gap
        - ↓ plasma CO3
    - In chronic renal failure in diabetes, the patient has hyponatremia, hyperaldosteronism, acidosis
    - Acidosis can lead to hyperkalemia or hyperchloremia
    - Clinical picture
        - Cardiovascular
            - HTN
            - Arrythmias
            - Heart Failure
            - Pericarditis
                - Fibrinous pericarditis
                    - Other causes of this are Rhuematic fever and Dressler's post MI
        - Respiratory
            - Congestion
            - Edema
        - Bone→renal osteodystrophy
        - Skin→uremic frost
        - Hematopoietic
            - Anemia—normocytic anemia (anemia of chronic dz)
            - Defective platelet aggregation
            - Leukopenia
                - b/c some of the toxins that are retained cause suppression of the bone marrow
    - Pathologic changes
        - Fibrinous peridarditis
        - Uremic pneumonitis
        - Osteitis fibrosa cystica (This is the bone change)
        - GI ulcers
    - Tests
        - Clearance
        - Cystatin C if present in urine → tubular damage
            - Cystatin C is only cleared through the tubules
        - Microalbuminemia → early diabetic nephropathy
- RENAL OSTEODYSTROPHY
    - A 55-year-old female with chronic renal failure (on dialysis for 8 years) presents with leg and back pain. The patient is found to have high PTH.
        - What happened here?
            - ↓ Phosphate filtration and excretion →↑ Serum phosphate ↑ PTH
            - ↑ Serum phosphate→ Suppress
            - Hydroxylation of 25-hydroxyvitamin D → ↓ Plasma levels of calcitriol (principal enhancer of calcium absorption from GI tract)
            - The above leads to hypocalcemia→ hyperparathyroidism
            - Hyperparathyroidism→ ↑ Osteoclasts activation → bone resorption→ ↑ Plasma calcium
            - *Result:* RENAL OSTEODYSTROPH



LAB ASSESSMENT OF RENAL FAILURE

- Urinalysis
  - Appearance
    - Normal straw color
    - Abnormal
      - Colorless
        - dilute urine
        - Low specific gravity
        - Tubular diseases
    - Milky → infections (pmn's)
    - Yellow-green → bilirubin
    - Red
      - vitamins/ food items
      - Hemoglobin
      - Myoglobin
    - Black → melanin
    - Dark orange→ liver problems
- Collection of urine:
  - wake up at 7am void and discard. Then from that point on until 7am the next day save every drop of urine.
  - for screening 1st morning voided specimen is best
    - Protein
    - specific gravity
    - nitrites
- For glucose, a post prandial specimen is better
- quantitative analysis:
  - 24 hr. Urine specimen is needed - preservatives needed will depend on substances to be tested.

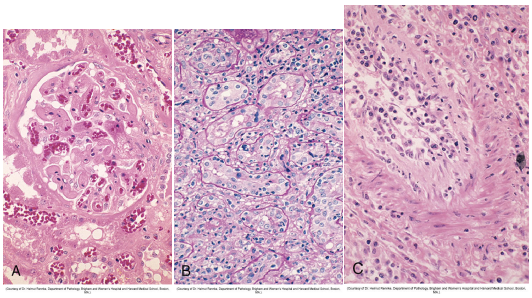
- Storage: urine should be examined fresh or refrigerated.
    - b/c at room temp the specimen can get messed up and not a true representation of the person's urine
- Cultures:
    - Cath
    - Clean catch midstream
        - Tell patient to clean themselves and then catch a specimen mid stream
- Volume
        - Normal 1200-1500 ml/24 hours
        - Oliguria <500 ml of urine daily
            - Dehydration
            - Renal disease
                - oliguria is the first stage of acute tubular necrosis
            - Obstruction
        - Polyuria >2000 ml/24 hours
            - Diabetes
                - Mellitus
                - Insipidus
            - Tubular renal diseases (acute or chronic)
                - Will also develop polyuria
    - Specific gravity (tells how concentrated the urine is)
        - Normal 1015-1025
        - Low s gravity
            - diabetes insipidus
                - associated w/ posterior pituitary problems
            - Tubular diseases
        - High s gravity
            - diabetes mellitus
            - Dehydration
    - pH variable with diet
        - except some crystal ppt in acidic pH (uric acid crystals) and some at alkaline pH (phosphate crystals that lead to the staghorn stone)
    - Chemistry:
        - Protein*
            - 1+ 250-500 mgm (24 hour)
            - 2+ 500-1000 mgm (24 hour)
            - 3+ 1000-2000 mgm (24 hour)
            - 4+ >2000 mgm (24 hour)
        - Glucose
            - Diabetes
            - Tubular Defect
            - ↓ Renal Threshhold
        - Ketones
            - Starvation
            - Diabetes
            - GASTROENTERITIS IN CHILDREN
        - Bilirubin
            - OBSTRUCTIVE JAUNDICE
        - Blood
            - Hemoglobinuria
            - UTI
            - Glomerular Dz
            - Interstitial nephritis
            - Tumors
            - Stones
        - Urobilinogen
            - Hemolyiss
            - Hepatitis (liver disease)

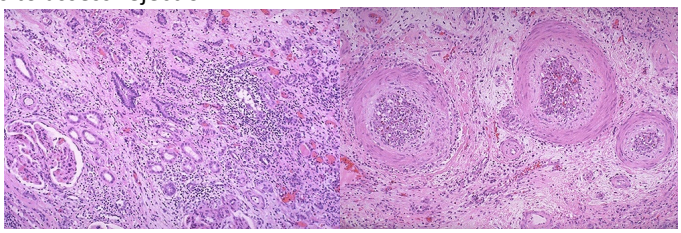
        - Nitrites
            - Associated w/ UTI's
            - BACTERURIA
            - also in UTI's note that you will see LEUKOCYTE ESTERASE.
                - So if you have a pt w/ WBCs, nitrites, and leukocyte esterase in the urine it is an infection.
                - But if you see just WBCs and not nitrites of leukocyte esterase then this is STERILE PYURIA which is **associated w/ papillary necrosis**
    - Microscopic examination
        - cells:
            - RBC → hematuria
            - WBC→ pyuria
            - Tubular cells → tubular necrosis
            - Squamous malignant cells
    - Crystals
        - Uric acid crystals—acidic urine
        - Magnesium, ammonium, Ca phosphate crystals→ alkaline urine
        - Calcium oxylate→ ethylene glycol intox
    - Casts:
        - RBC→ acute nephritic syndrome
            - 
        - WBC→ acute pyelonephritis
            - 
        - Granular→ acute **nephritic** syndrome
        - Hyaline→ chronic renal disease
        - Tubular/ MUDDY BROWN → acute tubular necrosis cells
    - Others
        - OVAL FAT BODIES → (tubular) cells loaded with lipid droplets seen in NEPHROTIC SX
    - Bacteria
    - Yeasts
- Glomerular functions
    - Clearance
        - Rate of urinary excretion of a substance/ the plasma concentration of that substance
        - if we have X amt in plasma how much do we clear per minute time
        - To estimate GFR
            - endogenous--creatinine
            - exogeneous--inulin
        - The amount of plasma cleared of the substance to account For the amount of substance excreted in the urine during a given period (usually expressed in mL/minute)
        - To calculate clearance, we have to know:
            - The Amt of substance excreted in urine
            - Plasma concentration of the substance
            - Formula
                - $C_x = (U_xV)/P$
                    - C_x = clearance
                    - U_x = concentration of substance in urine
                    - V = volume of urine/unit time
        - Creatinine clearance is what we use
            - creatinine clearance varies w/ gender and age (decreases as we get older)

- Glomerular filtration rate
  - Using exogenous substances
    - Inulin clearance is the gold standard
    - Normal 127 ml/min/1.73 m^2 ♂ MALE
    - Normal 118 ml/min/1.73 m^2 ♀ FEMALE
  - Using endogenous substances
    - Creatinine depends on:
      - Muscle mass
      - Tubular secretion
    - Urea depends on Diet
- Tubular functions
  - Electrolytes
    - K^+
      - Potassium excretion also impaired in renal function→ resulting in cardiac arrhythmia
    - Na
    - Chloride
    - In renal failure there is retention of Both Na^+ and water
  - Specific gravity (urine)
    - high SG= lots of electrolytes in the urine
  - Acid base balance
    - to see metabolic acidosis
      - Acidosis
        - Tubular damage = impaired secretion of ammonium
        - This results in impaired hydrogen ion reabsorption
        - This results in metabolic acidosis
          - ↑ anion gap
          - ↓ Plasma HCO3
- Endocrine function
  - erythropoietin
  - Calcium
  - Renin

RENAL TRANSPLANT

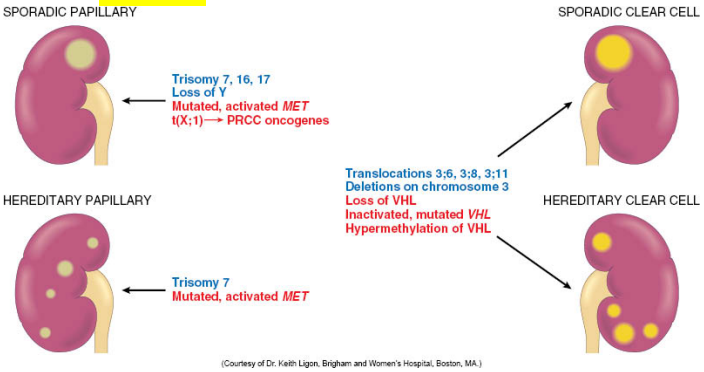
- Complications of renal transplantation
  - Surgical
    - hematoma
    - Leakage
  - Rejection
  - Cyclosporin toxicity
  - Recurrence of original disease
  - Graft nephropathy
- Rejection
  - Hyperacute rejection preformed antibodies → Acute vasculitis → Thrombosis→ Infarcts
- Acute rejection
  - Humoral → antibodies
  - Cellular→ t cells
  - Cellular infiltrates around tubules→ tubulitis
  - Cellular infiltrates Around vessels→ arteritis
  - Fibrinoid necrosis of vessels and glomeruli in humoral rejection
- Chronic rejection - fibrosis

- 

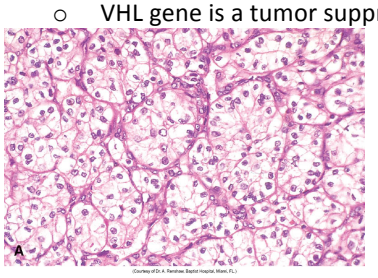
- Increasing graft survival:
  - HLA typing and matching
  - Immunosuppression of the recipient
  - Induction of transplantation tolerance
- Monitoring of transplant patient
  - Organ Function
    - Liver
    - Renal
    - Heart
  - Cyclosporin levels
  - T. Cell subsets to assess therapy and predict response
    - Cd4
    - Cd8
    - Cd3
  - Biopsies to assess rejection
    - 
- Cyclosporin effect
  - Nephrotoxicity
    - Tubular necrosis
    - Angiopathy
  - Hepatotoxicity
  - Lymphoma

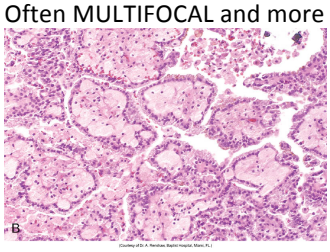
RENAL TUMORS

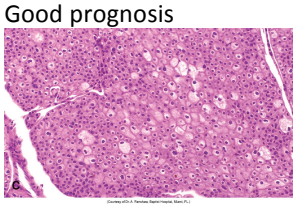
- **HARMATOMAS**
  - Harmatoma—tumor made of multiple mesenchymal tissues usually **benign** in nature
    - Angiomyolipoma: common benign tumor (w/single or multiple nodules) of the kidney and are composed of blood vessels, smooth muscle cells and fat cells → can lead to hematuria b/c of the angio component
      - Frequently associated with the genetic disease: TUBEROUS SCLEROSIS
        - Systemic disease
          - A neoplasms of kidney, skin, heart, and brain
            - RHABDOMYOMA is a tumor of the heart.
            - Positional loss of consciousness with MYXOMA (another tumor of the heart) associated with Carney syndrome
            - Other features of Carney Syndrome
              - Endocrinopathies and skin pigmentation
- **RENAL ADENOCARCINOMA:**
  - Most common PRIMARY tumor of the kidney in the adult population. Arises from the tubular epithelium.
  - Origin
    - Proximal convoluted tubules
  - Pathogenesis

        - Arise from renal tubules
            - EM
                - Brush borders
                - Large # of mitochondria-like proximal tubules
            - IF
                - Reacts to antibodies specific to brush border
    - Predisposing Factors:
        - HYDROCARBONS
            - Industrial exposure
        - Hormones
        - Lead
        - Irradiation
        - Viruses
        - TOBACCO
    - 

    - Most tumors are sporadic; 4% only are familial
        - Sporatic are usually single
        - Familial are usually multiple tumors in the same kidney
    - VON HIPPEL-LINDAU (VHL) SYNDROME
        - The gene implicated in both sporadic and familial cases of CLEAR-CELL CARCINOMA
        - VHL is a tumor suppressor gene
    - HEREDITARY PAPILLARY CARCINOMA
        - Autosomal dominant
        - Mutation in MET proto-oncogene
            - MET is activated—usually more aggressive
        - Usually bilateral
    - Clinical Picture
        - Painless Hematuria
            - Bladder also gives painless hematuria
        - Less common
            - Fever
            - Flank Pain
            - Colics
                - When they are trying to expel blood clots
            - Palpable flank Mass
            - Metastatic Dz
    - Lab findings
        - Anemia→ bleeding
        - Polycythemia→ production of EPO→ stimulates erythropoiesis
            - Will be flushed (purplish in color), have **itching** (especially when in a hot shower)
            - To diff tumor from polycythemia vera—polycythemia vera will have low EPO
        - Hypercalcemia—PARANEOPLASTIC SYNDROME
            - Due to ↑ levels of PTH-related protein
            - Hypercalcemia will cause mental problems, irritability, **severe constipation**
    - Dx
        - X-Rays
        - Angiography
        - Scan

- Spreads hematogenously through the RENAL VEIN
  - Can ascend all the way to the right side of the heart
- CLASSIFICATION
  - **Clear Cell**
    - Most common
    - Mutation of VHL gene
      - VHL gene is a tumor suppressor
    - 

      - have clear or granular cytoplasm.
      - Appear clear b/c they contain fat and glycogen—if you stain them for lipid they will stain positive
  - **Papillary Carcinoma**
    - Have a papillary growth pattern and affect the proximal tubules. Underlying genetic cause is a defect in the MET gene (a proto-oncogene on chrom 7)
    - 10-15% of renal cancers
    - Papillary growth pattern
    - Both sporadic and familial
    - Common associations
      - Trisomy 7 (FAMILIAL) and 17 and loss of Y in male patients (SPORATIC FORM)
        - Trisomy 7 in → familial form
          - Chromosome 7 encompasing MET locus (a protooncogene) activated
            - This protooncogene serves as tyrosine-kinase receptor for Hepatocyte growth factor
            - Hepatocyte Growth Factor and Scatter Factor → Growth, Cell mobility, and Invasion
    - Often MULTIFOCAL and more AGGRESSIVE than clear cell
    - 

  - **Chromophobe renal carcinoma**
    - Affect the cortical collecting duct, stain darkly and are characterized by loss of an entire chromosome)
    - 5% of renal cell cancers
    - Cells with pale eosinophilic cytoplasm
    - Hypodiploid cells
    - Good prognosis
    - 

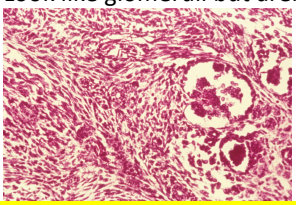
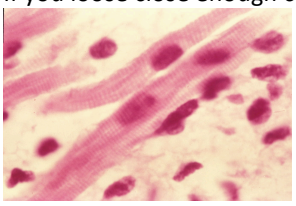
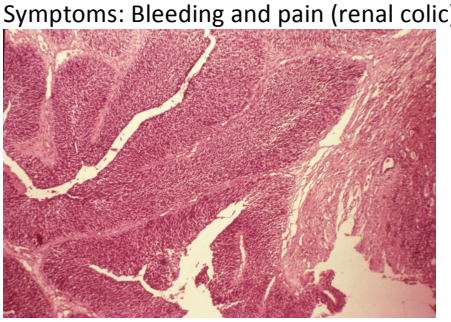
- STAGING
  - I. Confined To Kidney
  - II - Invasion To Fat But Confined To Gerota's Fascia
  - III
    - A. Invasion Of Renal Vein & Vena Cava

- B. Invasion Of LN
- C. Both A & B

- IV
  - A. Invasion Of Adjacent Organs Other Than Adrenal Gland
  - B. Distant Metastasis

- PROGNOSIS
  - Without venous extension (relatively good)
    - 60% 5 year survival
    - 50% 10 year survival
  - With venous extension
    - 30% 5 year survival
    - 25% 10 year survival
  - Other factors
    - # Of tumors—many of multiple
    - size—bigger is worse
    - local extensions, capsule & fat

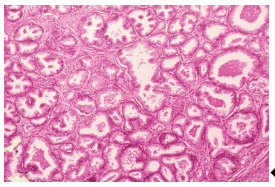
- **WILMS TUMOR**
  - EPIDEMIOLOGY
    - One in very 10,000 CHILDREN in the US
    - Peak age 2-5
  - GENETICS:
    - Associated with 3 syndromes
      - I. WAGR
        - Wilms Tumor
        - Aniridia (no irises)
        - Genital anomalies
        - Mental Retardation
        - Cause: Deletion of llp13 tumor associated gene WT_1 → Frameshift mutation in WT_1
      - II. DENYS-DRASH SYNROME
        - Gonadal dysgenesis
        - Diffuse mesangial sclerosis→ Renal Failure
        - Gonadoblastoma
        - Wilms Tumor
        - Cause: Missense mutation of WT_1
      - III. BECKWITH-WIEDEMAN SYNDROME
        - Organomegaly
        - Macroglossia
        - Hemhypertrophy
          - One hand is bigger than the other
    - SPORATIC cases of Wilm's Tumor
      - Associated w/ mutation of β-catenin gene
  - CELL OF ORIGIN
    - Embryonic renal cells displaced during development, but retaining the ability to grow and differentiate into various types of tissues
  - CLNICAL PICTURE
    - Abdominal Mass 90%
    - Hypertension 0-60%
    - Pain 20-30%
    - Anorexia 15%
    - Nausea 15%
    - Vomiting 15%
    - Fever 5-10%
  - Dx:
    - X-Ray
    - Arteriograms
  - LAB FINDINGS
    - ↑ Erythropoietin levels
      - use these levels to monitor therapy, recurrence and metastasis

        - Do extremely well with combination of chemo and surgery
    - MORPHOLOGY
        - Gross
            - Large
            - Gray
            - Firm
            - Commonly the capsule ruptures and you get extension to kidney, omentum, etc
        - Microscopic
            - 3 components
                - **Epithelial Abortive Glomeruli**
                - Look like glomeruli but aren't glomeruli
                - 
                - **STROMAL RHABDOSARCOME (MOST COMMON)**
                - If you loose close enough can see elements of malignant skeletal muscle
                - 
                - **Embyonal**
                - Very undifferentiated embryonal tissue.
    - SPREAD
        - Lungs
        - Liver
        - LN
    - PROGNOSIS
        - Good if dz <2 years w/ combo of surgery and chemo
        - Depends on size and extension
- **RENAL PELVIS TUMOR**
    - 50% multicentric Transitional cell carcinomas
    - Symptoms: Bleeding and pain (renal colic)
    - 

DISEASES OF THE PROSTATE

- **INFLAMMATIONS**
    - Acute Bacterial Prostatis
        - Organisms—most common E. Coli
        - Route of Entry: Intraprostatic reflex of urine, or instrumentation
        - Clinical picture: Fever, chills dysuria, usually in older men
        - Dx:
            - U/A: nitrites and LE

        - Urine culture, rectal exam
    - Chronic bacterial prostatitis
        - Preceding illness = recurrent urinary tract infections
        - Clinical picture = low back pain
            - Low back pain think of vascular things (aortic aneurysm), hematological things (multiple myeloma)
        - Dx: leukocytosis and dysuria, may see WBC in urine
        - Positive cultures of prostatic secretions
- **CHRONIC ABACTERIAL PROSTATITIS**
    - Clinically same symptoms as chronic bacterial prostatitis
    - No history of recurrent urinary tract infections
    - Benign prostatic diseases
        - 20% of men 40 years of age
        - 70% of men 60 years of age
        - 90% of men 70 years of age
    - Pathogenesis
        - Men normally don't get UTI unless there is an obstruction, usually from BPH--↑ prostate → ↑ obstruction→ ↑ stagnation → ↑ infection
        - Androgens = Dihydrostestosterone (DHT) metabolite of testerone is the mediator of prostatic growth
        - Testosterone 5 alpha Reductase (enzyme present in stromal cell) converts testosterone → DHT binds to Nuclear androgen receptors 6→ signal Transcription of growth factors→ leading to stromal and glandular cells → Stromal and glandular hyperpasia of the prostate
        - Inhibitors of 5 alpha Reductase→ ↓ DHT→ ↓ hyperplasia
        - Estradiol also enhances hyperplasia by inducing an ↑ in androgenous receptors→ DHT acts on these receptors to cause the growth → Cells more susceptible to DHT
            - Note estradiol ↑ in aging men
    - Clinical picture
        - Difficulty in urination
        - Urine retention
            - This is a medically emergency
        - Frequency
        - Nocturia
        - Weak stream
        - Dysuria
    - Pathology: Stromal and glandular hyperplasia
    - Complications
        - lower and upper urinary tract infections
        - Not premalignant tumors
            - Has nothing to do w/ prostate cancer
- TUMORS
    - Incidence: most common in men
    - Men >50 years
    - Racial differences: lower incidence in Asians
    - Environmental factors: fat consumption
    - Hormonal→ ↑ level testosterone
    - Familial tendency chromosome 1q 24-25
        - Usually see these in younger age
    - Morphology
        - 70% of cases→ peripheral (posterior)
        - Spread
            - Direct extension
            - Lymphatic
            - Worst is Bones mostly → spines
                - Low back pain
        - Histology → adenocarcinoma
            - Malignant –Very little stroma and small glands (no pleomorphism)

-  ←no stroma so malignant
  - Benign – irregular, dilated glands with lots of stroma in between
    -
- Clinical picture
  - Most of the time asymptomatic unless bone metastasis
- Dx
  - Rectal examination – firm mass in posterior aspect of the prostate
  - Elevated PSA (prostate-specific antigen)
    - The value of PSA is under scrutiny. 1 abnormal value is not diagnostic
- Grading:
  - 5 grades
  - Gleason (PROSTATE GRADING) most predominant and subdominant pattern
    - Gleason grading of the prostate→Look at how differentiated are the cells in each of the tiny glands.
    - Look at the bx and Look at most common pattern.
      - If most glands are lined by nice differentiated cells, give gleason 2.
      - If look at biopsy and most glands are really ugly and undifferentiated, give gleason 5
    - Then, look at the 2nd most common pattern in the same biopsy and say is it 2,3,4, or 5.
    - Then add the numbers together..
  - Most differentiated 2 and least differentiated 10 (5+5)
- Staging (Just know ABCD)
  - A = microscopic not palpable
    - A_1 < 5% of tissue examined
    - A_2 multiple foci or Gleason >4
  - B = palpable on rectal exam
    - B_1 < 1.5 cm in lobe
    - B_2 > 1.5 multiple nodules in both lobes
  - C = extracapsular extension
    - C_1 →seminal vesicle, no pelvic wall
    - C_2 → fixed to pelvic wall
  - D = metastic
    - D_1 → limited to 3 pelvic nodes
    - D2 → distant metastasis (bones, etc.)
      - Usually met to the bones
- Markers
  - PSA
    - PSA will tell you if you should biopsy, but doesn't help with metastatic disease.
  - Prostatic acid phosphatase
    - In metastatic prostate cancer to the spine, prostatic acid phosphatase and alkaline phosphatase will be elevated. These are osteoblastic lesions they form bone they don't destroy it
      - 65 yo man with low back pain and elevated alkaline phosphatase think about bone spread form prostatic cancer.
  - Bone alkaline phosphatase—explained above
- Therapy
  - Surgery
  - Radiotherapy
  - Hormones

PATHOLOGY OF THE URINARY BLADDER

- EXSTROPHY (Congenital anomaly)
  - **Congenital Vesicocutaneous fistula**
    - Incomplete closure of anterior abdominal wall
    - Incomplete closure of anterior bladder wall
    - Exposure of bladder mucosa to the outside
    - **Cause overgrowth of cloacal membrane**
    - **Complications**
      - Acute and chronic infections
      - Metaplastic changes
      - Risk of neoplastic transformation
    - Fix w/ surgery
- INFLAMMATORY DISEASES
  - **Infections:** Organism *E. Coli* most common
  - **Clinical Picture:**
    - Urgency
    - Dysuria
    - Hematuria
    - Pain
  - **Dx:**
    - Urinalysis
      - Many WBCs
      - Many bacteria
      - Nitrite positive
      - Leucocyte esterase positive
      - If casts with nitrite and LE, then its acute pyelonephropathy
        - If no casts= cystitis
    - Urine Culture will give dx
  - Pathology
    - acute inflammation, if persistent, can lead to chronic changes
      - Vesicoureteral reflux can lead to pyelo
  - Course – recurrent
  - Complications
    - Upper urinary tract infections
    - Metaplastic changes
- CHRONIC INTERSTITIAL CYSTITIS—HUNNER'S ULCER
  - **Middle age women**
    - Suprapubic pain (Very painful)
    - Frequency
    - Urgency
    - Does not respond to antibiotics
  - Edema, ulcerations and granulation tissue
  - **Pathologenesis**
    - Thought to be autoimmune
- **MALACOPLAKIA**
  - Usually seen in immunosuppressed patients (cancer, transplant, etc)
  - **Raised mucosal plaques made of:**
    - Large foamy macrophages PAS positive
    - Occasional giant cells
    - Lymphocytes
    - **INTRACELLULAR CONCRETIONS "MICHAELIS-GUTMAN BODIES"**
      - Rich in iron
  - **Pathogenesis:** chronic infections
- **METAPLASTIC CHANGES SEE IN INFLAMMATORY DZ**
  - **CYSTITIS GLANDULARIS AND CYSTITIS CYSTICA**
    - **Definition**

- Downward growth (just this then **cystitis cystica**) of transitional epithelium "Brun nests" into lamina propria with metaplastic changes (most commonly glandular—if metaplastic changes then **cystitis glandularis**)
    -
- **Incidence**
  - Occasionally seen in normal bladder
  - Usually in chronically irritated bladder
- **Complications**
  - **Adenocarcinoma** with the cystitis glandularis

- NEOPLASMS
  - **Epidemiology**
    - Male >Female 3:1
  - **Predisposing factors**
    - Cigarette smoking
    - Industrial exposure
      - 2 – Naphthylamine
    - Schistosoma hematobium
      - No transitional cell carcimoma here but will see squamous cell carcinoma
    - LONG TERM USE OF ANALGESICS
    - Long term exposure to cyclophosphamide
  - Indication of genetic alterations especially in chromosome 9.
    - Several other mutations have also been described
  - **Clinical picture**
    - painless hematuria
  - **Course: Recurrence is common**
    - Course depends on grade & stage
    - Presence of blood group antigen on the tumor cells themselves is associated with good prognosis
    - Presence of chromosome abnormalities and gene mutation; also if you lose the blood group antigen is associated with poor prognosis
  - **TRANSITIONAL CELL CARCINOMA:**
    - These tumors can spread to the kidney
    - **Grading of Urothelial (Transitional Cell) Tumors**
      - The more it looks like the normal bladder lining the less the grade. The more undiff it look the more the grade
        - Grade 1 – looks identical to lining→Papillary
        - Grade 4 – very undifferentiated cannot tell it is bladder

WHO Grading	**ISUP Consensus**
Papilloma	Urothelial Papilloma
TCC Grade I	Urothelial neoplasm of low malignant potential
TCC Grade II	Urothelial carcinoma, low grade
TCC Grade III	Urothelial carcinoma, high grade

    - **Pathologic Stages of Bladder Carcinoma**
      - Stage 1 is in situ (it didn't no cross the BM)
        - ↑ in stage the more invasive it becomes
      - T- tumor itself, how deep
      - N – nodes
      - M - metastasis

Depth of Invasion	**AJCCC/UICC**
Noninvasive papillary	Ta
Noninvasive, flat	TIS
Lamina propria	T1
Superficial muscularis propria	T2
Deep muscularis propria	T2a
Perivesical fat	T3b
Lymph node metastases	N1-3*
Distant metastases	M1

    - **Low grade tumors**
      - Papillary—good prognosis

        - DNA → Diploid
        - No or limited chromosomes or gene abnormalities
        - Retain blood group ANTIGEN
    - **High grade tumors**
        - Papillary or **nodular**
        - DNA → aneuploidy
        - Marked anaplasia
        - High frequency chromosomes and gene abnormalities
        - **Lack blood group antigens**
- **SQUAMOUS CELL CARCINOMAS:**
    - In countries with **endemic schistosomiasis**
        - Not papillary
        - Usually invasive
    - **Adenocarcinoma**
        - Rare
        - Associated w/ cystitis glandularis
    - **Mesenchlymal tumors**
        - Benign Leiomyoma
        - Malignant sarcoma very rare
    - **Secondary tumor**
        - By extension form nearby organs
        - Rectum – uterus – cervix – prostate